



# EVIDENCE-BASED DERMATOLOGY

THIRD EDITION

Edited by  
**Hywel C. Williams**  
Michael Bigby  
Andrew Herxheimer  
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# **Evidence-based Dermatology**

Third edition

# Dedication

We, the editors, dedicate this book to our patients who have helped us to understand what it is really like to have a skin disease, and who have helped us to identify the questions that matter to them. Evidence-based dermatology starts with patients and ends with patients. If we lose our compassion for patients, we become a sounding brass or a tinkling cymbal.



# Evidence-based Dermatology

**Third Edition**

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# Foreword

Twenty-eight years ago, when drafting an introductory chapter for a book on the effects of care during pregnancy and childbirth [1], I decided to use contrasting quotations from a distinguished statistician and a distinguished dermatologist. In 1952, Austin Bradford Hill had written [2]:

In my indictment of the statistician, I would argue that he may tend to be a trifle too scornful of the clinical judgement, the clinical impression. Such judgements are, I believe, in essence, statistical. The clinician is attempting to make a comparison between the situation that faces him at the moment and a mentally recorded but otherwise untabulated past experience.

Twenty years later, Sam Shuster coined the memorable phrase [3]:

Lies, damned lies and clinical impressions.

My draft went on to discuss the fundamental importance and great dangers of clinical impressions: in obstetric practice they have led both to important therapeutic discoveries and to iatrogenic disasters. I doubt that people treating skin disease have the capacity to do unintended harm on the scale achieved by obstetricians and neonatologists, but I also doubt there is any justification for complacency in matters of dermatological therapy.

The huge variability that exists in the management of common chronic skin diseases is clear evidence of collective uncertainty about the effects of alternative management strategies, even if a majority of individual clinicians are certain that they are doing the right thing. For example, I gather that fumaric acid esters have been used widely to treat psoriasis for over 40 years in Germany and the Netherlands, but that, although their use is supported by good evidence [4], they have hardly been used at all anywhere else. Some patients with warts are being put to the inconvenience (and expense) of attending hospital for cryotherapy; yet there is no strong evidence to suggest that they would be worse off treating their warts at home with salicylic acid paints [5]. Topical corticosteroid preparations like bethamethasone valerate are traditionally used twice daily, yet there is no good evidence to show that twice-daily applications are more effective than once-daily applications. Furthermore, once-daily applications are easier for people with eczema, they may result in fewer side effects, and they are also less costly [6]. As professionals are concerned to do more good than harm to their patients, all who treat skin disease have a duty to reduce uncertainty about the relative merits of alternative treatments by paying attention to the results of well-designed research.

To do right by their patients, people treating skin disease need to know what they know and what they don't know. This book tries to help them. Unlike traditional textbooks, it contains a toolbox section that describes the methods that have been used to review the evidence upon which conclusions about the effects of treatments have been based, and gives references to more detailed reports of the systematic reviews on which much of the text has drawn.

There is no consensus about the materials and methods that should be used to assemble evidence to support treatment recommendations published in textbooks and review articles, nor even

about the principles of systematic reviews. One senior dermatologist, for example, has written [7]:

The idea of a systematic review is a nonsense, and the sooner those advocates of it are tried at the International Court of Human Rights at the Hague (or worse still, sent for counselling), the better.

Unfortunately, those who express reservations about applying systematic approaches to the synthesis of research evidence tend not to outline the alternative strategies that they implicitly deem preferable. This is a serious matter because it has been shown that reviews using explicit methods reach conclusions that differ from traditional reviews, with implications that can be matters of life or death [8]. In dermatology, too, the conclusions of reviews in which efforts have been made to reduce biases and the effects of chance can differ from those reached in traditional reviews [9], and Cochrane systematic reviews have been shown to be higher quality than other systematic reviews [10]. In the light of this evidence, I believe that continued acquiescence in reviews that have not attempted to minimize biases and, where possible and appropriate, the effects of chance is not only scientifically unacceptable but also ethically highly questionable [11].

The contributors to this book have tried to control biases and – where they judged it appropriate – they have also reduced the effects of the play of chance by using statistical synthesis to analyze the results of similar but separate studies. As ways of improving the materials and methods used in such research synthesis are developed further, researchers will apply them, taking advantage of the potential offered by electronic media to publish full and transparent accounts of their work, and to respond to new data and suggestions for improving their analyses.

This third edition of *Evidence-based Dermatology* has extended coverage of topics from the second edition to include several additional and important skin disorders, such as molluscum contagiosum, pityriasis versicolor, onychomycosis, and vulval lichen sclerosus. And in the introductory section of the book, there are new chapters on outcome measures and qualitative research.

In laying bare just how much cannot be known on the basis of reliable evidence, the contributors to this book have also posed a very great challenge to everyone involved in treating skin disease. Can it be that a modest reduction in “doctor-assessed itch” is really the only demonstrable beneficial effect of the widespread use of evening primrose oil for people with eczema [12]? The book exposes the dearth of reliable studies addressing questions and outcomes that matter to patients, and it reveals the extent to which perverse incentives distort the dermatological research agenda. Those suffering from skin disease have every right to expect more from clinicians, researchers, and those who fund research. This book should help to provoke them to do better.

Professor Sir Iain Chalmers  
Oxford, UK  
2014

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# Preface

When I started with the first edition of this book in 2001, evidence-based dermatology was a risky and controversial subject. It was new and threatening to some, and the topic was barely mentioned at large dermatology meetings where the case report was still king. Nowadays, everyone seems to be blurting out the word “evidence” in every other sentence. But what does it really mean in relation to good clinical dermatology care?

I am confident that this book will help you to make that bridge between good external evidence and the care of individual patients. Such integration is not easy in the messy realities of everyday life – the key is to try and to continue to enjoy lifelong learning.

For those of you new to *Evidence-based Dermatology*, you will find it a *different* sort of book to the usual textbook. Different in that we start the book by providing you with a detailed “toolbox” to help you understand the basic rudiments of *practicing* evidence-based dermatology. Our clinical chapter contributors then follow a common structure when summarizing the evidence base for different skin diseases. That structure begins with a clinical scenario, followed by clinical questions that lead to an evidence summary, based on the best possible evidence, such as systematic reviews and randomized controlled trials. Each summary includes a description of the possible benefits and drawbacks of individual treatment approaches followed by a view on the clinical implications of that evidence. It is a lot more work to write in this way than to let experts write what they like, but the success of the first two editions of this book suggests that you, the reader, appreciate such an approach. We have taken care, where possible, to separate the evidence found in studies from our opinions about that evidence, and we have tried

to help the reader by summarizing the key points at the end of each chapter.

For those of you familiar with the first and second editions of *Evidence-based Dermatology*, welcome back. In addition to providing evidence updates to chapters from previous editions, several new chapters appear in this third edition. In the toolbox section, there is now a chapter explaining all about comparative effectiveness research, another on outcome measures, and another describing qualitative research.

In the clinical section, there are new evidence summaries on molluscum contagiosum, pityriasis versicolor, onychomycosis, dermal fillers and wrinkles, and vulval disorders.

This third edition of *Evidence-based Dermatology* has been a labor of love for me, my associate editors, and chapter contributors, and I wish to thank them all for their efforts. None of us have contributed to this book for the money, but because of our motivation to create a stable record of what evidence-based dermatology is and how it can be applied to clinical practice. We have strived to keep the book as patient based as possible by discussing the evidence around commonly encountered patient scenarios. At the end of the day, it is patients who are at the heart of evidence-based dermatology. Please use this book in your clinic, rather than the library. If the book ends up dirty, torn, and fingered from daily use, we will be delighted.

Hywel Williams  
March 2014



# About the companion website

Evidence-based Dermatology: Companion Website

Additional resources to accompany this book are available at:

**[www.evidencebasedseries.com/dermatology](http://www.evidencebasedseries.com/dermatology)**

**Included on the site:**

- **Extra tables of trial results**

Web Table 19.1 Retinoid RCTs.

Web Table 19.2 BP versus placebo/retinoid RCTs.

Web Table 19.3 Azelaic acid RCTs.

Web Table 19.4 Oral antibiotics versus placebo RCTs.

Web Table 19.5 Head to head oral antibiotic RCTs.

Web Table 19.6 Topical versus vehicle antibiotics.

Web Table 19.7 Topical versus topical antibiotics.

Web Table 19.8 Oral versus topical antibiotics.

Web Table 19.9 Combination antibiotic RCTs.

Web Table 19.10 Antibiotic/retinoid combination RCTs.

Web Table 19.11 BP/antibiotic combination RCTs.

Web Table 19.12 Oral isotretinoin RCTs.

<http://www.evidbasedderm.com>

Web Table 24.1 Emollients for the treatment of atopic eczema.

Web Table 24.2 Topical steroids versus placebo in atopic eczema: results of RCTs.

Web Table 24.3 Oral antihistamines for atopic eczema.

Web Table 24.4 RCTs of dust mite reduction for the treatment of atopic eczema.

Web Table 24.5 Table of elimination diets in the treatment of those with established atopic eczema.

Web Table 24.6 Randomized controlled trials of probiotics in the treatment of atopic eczema.

Web Table 24.7 Randomized controlled trials that have evaluated treatments for clinically infected atopic eczema.

Web Table 24.8 Randomized controlled trials that have evaluated antiseptics for atopic eczema.

Web Table 24.9 Randomized controlled trials that have evaluated topical steroid/antibiotic combinations for non-infected atopic eczema.

<http://www.evidbasedderm.com>

Web Table 74.1 Table of systematic reviews included.

Web Table 74.2 Skin conditions included.

<http://www.evidbasedderm.com>

- **Glossary of terms**



# **PART I**

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## **The concept of evidence-based dermatology**

Andrew Herxheimer, editor



## CHAPTER 1

# The field and its boundaries

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### Introduction

Evidence-based medicine (EBM) represents the best way of linking and integrating clinical research with clinical practice. The results of clinical research should inform clinical practice. Ideally, whenever a clinical question has no satisfactory answer it should be addressed by clinical research. Since clinical questions are innumerable and resources are limited, the process needs some control, and priorities should be set using explicit and verifiable criteria. The public and purchasers have to be involved at this stage, and health needs and expectations in any given clinical area should be analyzed and taken into account. In many instances, confirmatory studies are needed and systematic reviews can be used to summarize study results, or to explore results in specific subgroups with a view to further research. The results of clinical research should be applied back to the individual patients in the light of their personal values and preferences. Communicational skills and patient understanding are key issues in this respect. In the real world, forces other than those involved in such an ideal process often distort research priorities and questions. For example, strong industrial and economic interests partly justify the lack of data on rare disorders or on common disorders if they occur mainly in poorer countries. This book may help to identify the more urgent questions that lack a satisfactory answer by summarizing for physicians (and patients) the best evidence available for the management of a large number of skin disorders – excluding sexually transmitted diseases, which are not regularly cared for by dermatologists. It can be thus be a starting point for rethinking the clinical research priorities in patient-oriented dermatology.

### What is special about dermatology?

The skin is not a simple inert covering of the body but a sensitive dynamic boundary and is an important organ of social and sexual contact. Body image is deeply rooted within the culture of any given social group and is profoundly affected by the appearance of the skin and its associated structures. The role skin appearance plays in

any given society is best understood from an anthropological perspective and using a narrative qualitative approach. This area is rather neglected in dermatological curricula.

Extensive disorders affecting the skin may disrupt its homeostatic functions, ultimately resulting in “skin failure,” needing intensive care. This is rare, but may happen, for example, with extensive bullous disorders or exfoliative dermatitis. The commonest health consequence of skin disorders is connected with the discomfort of symptoms – such as itching and burning or pain, which often accompany skin lesions and interfere with everyday life and sleep – and with the loss of confidence and disruption of social relations that visible lesions may cause. Feelings of stigmatization and major changes in lifestyle caused by a chronic skin disorder such as psoriasis have been repeatedly documented in population surveys [1,2].

### A vast array of clinical entities

Unlike most other organs that usually count around 50–100 diseases, the skin has a complement of 1000–2000 conditions, and over 3000 dermatological categories can be found in the International Classification for Disease version 10 (ICD-10). Part of the reason is that the skin is a large and visible organ. Beside disorders primarily affecting the skin, many major systemic diseases (e.g., of vascular and connective tissue) have cutaneous manifestations. Currently, the widespread use of symptom-based or purely descriptive terms, such as parapsoriasis or pityriasis rosea, reflects our ignorance and limited understanding of the causes and pathogenetic mechanisms of a large number of skin disorders. We still lack consensus on a detailed lexicon of dermatological terms for use in research and everyday clinical practice.

The ICD-10 revision dates back over 20 years to 1990. The new ICD-11 version due in 2014 should improve consensus. This review capitalizes on what three significant initiatives have achieved: (1) the Dermatologischer Diagnosenkatalog published in German-speaking countries by the Deutsche Dermatologische Gesellschaft and in English by the International League of Dermatological Societies; (2) the British Association of Dermatologists' diagnostic

index, first published in 1994 and updated annually since then; and (3) the Dermatology Lexicon Project, developed with a grant from the US National Institutes of Health, first published in 2005 and now supported by the American Academy of Dermatology [3].

### Extremely common disorders

Skin diseases are very common in the general population. Prevalence surveys have shown that they may affect 20–30% of the general population at any one time [4]. The most common diseases are also the most trivial ones. They include such conditions as mild eczematous lesions, mild to moderate acne, benign tumors and angiomas lesions. More severe skin disorders that can cause physical disability or even death are rare or very rare. They include, among others, bullous diseases, such as pemphigus, severe pustular and erythrodermic psoriasis, and such malignant tumors as malignant melanoma and lymphoma. The disease frequency varies according to age, sex, and geographic area. In many cases, skin diseases are trivial health problems compared with more serious medical conditions. However, as already noted, because skin manifestations are visible they may distress people more than do more serious medical problems. The issue is complicated because many skin disorders are not a yes or no phenomenon but occur in a spectrum of severity. The public's perception of what constitutes a "disease" requiring medical advice may vary according to cultural issues, the social context, resources, and time. Minor changes in health policy may have a large health and financial impact simply because many people may be affected. For example, most of the campaigns conducted to raise public awareness of skin cancer has greatly increased in the number of people having benign skin conditions such as benign melanocytic nevi evaluated and excised [5].

### Large variations in terms of health-care organization

Countries differ greatly in the way in which their health services deal with skin disorders. These variations are roughly indicated by the density of dermatologists ranging, in Europe, from about 1:20 000 in Italy and France to 1:150 000 in the UK.

In general, only a minority of people with skin diseases seek medical help, while many opt for self-medication. Pharmacists have a key role in advising the public on the use of over-the-counter products. Primary care physicians seem to treat most of those seeking medical advice. Primary care of dermatological problems is ill defined and overlaps with specialist activity. Everywhere the dermatologist's workload is concentrated in the outpatient department. Despite the vast number of skin diseases, just a few categories account for about 70% of all dermatological consultations [6].

Generally speaking, dermatology requires a low-technology clinical practice. Clinical expertise depends mainly on the ability to recognize a skin disorder quickly and reliably, which, in turn, depends largely on awareness of a given clinical pattern, based on previous experience and on the practiced eye of a visually literate physician [7]. The process of developing "visual skill" and a "clinical eye" is poorly understood, and these skills are not formally taught.

### Topical treatment may be possible

A peculiar aspect of dermatology is the possible option for topical treatment. This treatment modality is ideally suited to localized lesions, the main advantage being the restriction of the effect to the site of application and the limitation of systemic side effects. A

topical agent is usually described as a vehicle and an active substance, the vehicles being classified as powder, grease, liquid, or combinations such as pastes and creams.

Much traditional topical therapy in dermatology has been developed empirically with so-called magistral formulations. Most of these products seem to rely on physical rather than chemical properties for their effects, and it may be an arbitrary decision to consider one specific ingredient as the "active" one. Physical effects of topical agents may include detergency, hydration, and removal of keratotic scales. The border between pharmacological and cosmetic effects may be blurred, and the term "cosmeceuticals" is sometimes used [8]. In addition to drug treatment, various non-drug treatment modalities exist, including phototherapy or photochemotherapy and minor surgical procedures such as electrodesiccation and cryotherapy. Large variations in treatment modalities for the same condition mainly reflect local traditions and preferences [9].

### Limitations of clinical research

As in other disciplines, the last few decades have seen an impressive increase in clinical research in dermatology. However, the upsurge of clinical research has not been paralleled by methodological refinements; for example, the quality of randomized control trials (RCTs) in dermatology seems to fall well below the usually accepted standards [10]. Innovative thinking is needed in dermatology to make clinical research address the important issues and not simply ape the scientific design.

### Disease rarity

In at least 1000 rare or very rare skin conditions no single randomized trial has been conducted. These conditions are also those carrying a higher burden of physical disability and mortality. Many of them have an annual incidence rate of below one case per 100 000 and frequently below one case per million. International collaboration and institutional support are clearly needed, but so far such efforts are very few.

### Patients' preferences

One alleged difficulty with mounting randomized clinical trials in dermatology is the visibility of skin lesions and the consideration that, much more than in other areas, patients self-monitor their disease and may have preconceptions and preferences about specific treatment modalities [11]. The decision to treat is usually dictated by subjective issues and personal feelings. There is a need to educate physicians and the public about the value of randomized trials to assess interventions in dermatology. Motivations and expectations are likely to influence clinical outcomes of all treatments, but they matter more in situations where "soft end-points" matter, as in dermatology. Commonly, more than 20% of patients with psoriasis entering randomized clinical trials "improve" on placebo independently of the initial disease extension [12]. Motivations are equally important in pragmatic trials evaluating different packages of management, such as in the comparison of a self-administered topical product for psoriasis with hospital-based therapy like phototherapy. Traditionally, motivation as a characteristic of the patient that is assumed not to change with the nature of the intervention. However, it is more realistic to view motivation in terms of the "fit" between the nature of the treatment and the patient's wishes and perceptions, especially with complex interventions requiring the patient's active participation [13]. The public is



inundated with uncontrolled and sometimes misleading or unrealistic messages on how to make the body look better. The design and analysis of clinical trials must properly consider patients' motivations and what they are told.

### The use of placebo in randomized control trials

Too many placebo-controlled RCTs are conducted in dermatology even when alternative therapies exist [14,15]. As a consequence, many similar molecules used for the same clinical indications can be found in some areas; for example, topical steroids. Many regulatory agencies still regard placebo controls as the "gold standard." There is a need to establish criteria for the use of placebo in dermatology. They should be used with the active and informed participation of the public and should be considered by ethics committees and regulatory agencies. "Pragmatic" randomized trials conducted under conditions close to clinical practice and contrasting alternative therapeutic regimens are urgently needed to guide clinical decisions.

### Long-term outcome of chronic disorders

Several major skin disorders are chronic conditions where no cure is currently available. Whenever a definite cure is not reasonably attainable, it is common to distinguish between short-term, intermediate (usually measurable within months), and long-term outcomes. Long-term results are not simply predictable from short-term outcomes. Many skin disorders wax and wane over time, and it is hard to define what represents a clinically significant long-term change in the disease status. This is even more difficult than defining outcome for other clinical conditions, such as cancer or ischemic heart disease, where death or major hard clinical end-points (e.g., myocardial infarction) are of particular interest. In the long term, the way the disease is controlled and the treatment side effects are vitally important, and simply and cheaply measured outcomes applicable in all patients are more appropriate. These may include the number of patients in remission, the number of hospital admissions or outpatient consultations, and major disease flare-ups. Drop-outs merit special attention since they may strongly reflect dissatisfaction with treatment.

### Self-control design

Study designs that are often used at a preliminary stage in drug development are *within-patient control studies*; that is, crossover and self-controlled studies or simultaneous within-patient control studies. In dermatology they are also used, albeit improperly, at a more advanced stage. In a survey of more than 350 published RCTs of psoriasis, a self-controlled design accounted for one-third of all the studies examined and was relied on at some stage in drug development [14]. The main advantage of a within-patient study over a parallel concurrent study is statistical. A within-patient study attains the same statistical power with far fewer patients, and at the same time reduces variability between the populations 'confronted' [15]. Within-patient studies may be useful when studying conditions that are uncommon or show high degree of patient-to-patient variability. On the other hand, within-patient studies impose restrictions and artificial conditions, which may undermine validity and generalizability of results and may also raise some ethical concern. The washout period of a crossover trial as well as the treatment schemes of a self-controlled design, which entails applying different treatments to various parts of the body, do not seem to be fully justifiable from an ethical point of view. Clearly, the impractical treatment modalities in self-controlled studies or the washout

period in crossover studies may be difficult for the patient to accept. Drop-outs may have more pronounced effects in a within-patient study than in other study designs because each patient contributes a large proportion of the total information. The situation is compounded in self-controlled studies, where the dropping out from the study may be caused by observing a difference in treatment effect between the parts into which the patient has been "split up." In this case, given that drop-outs are related to a difference in treatment effect between interventions, the effect of the intervention is liable to be underestimated.

### The increasing role of industry-sponsored trials

The pharmaceutical industry's influence on medical research has increased enormously in the last decades. Dermatology is no exception. As indicated by the European Dermatoepidemiology Network psoriasis project, only a quarter of all randomized clinical trials published on psoriasis from 1977 to 2000 have been conducted without direct pharmaceutical companies' sponsorship, and the proportion of sponsored trials has increased dramatically in more recent years [14,16]. Evidence from systematic reviews show that published studies funded by pharmaceutical companies are several times more likely to have results favorable to the company than studies funded from other sources [17].

Selective presentation of scientific data, statements by opinion leaders in sponsored symposia and involvement of patient organizations in sponsored campaigns are among the promotional strategies adopted to expand the market once limited clinical evidence has been collected on a new agent. Heavy marketing competition has been paralleled by a cycle of increasing collusion between physicians, academic opinion leaders, patients' organizations, researchers, and industrial interests [18,19].

The recognition of the problems involved with new drug registration and the lack of long-term data on effectiveness and safety have prompted the starting of registries and postmarketing surveillance programs closely linking prescription to the provision of patient data at first drug prescription and on a regular basis subsequently during a predefined follow-up period. Psoriasis registries are a successful example [20].

### The limitations of systematic reviews

The large number of clinical studies in dermatology and the lack of consensus on the management of many skin disorders point to systematic reviews as a way to improve the evidence and guide clinical decisions. However, systematic reviews alone cannot be expected to overcome the methodological limitations in dermatological research we have pointed to. On the contrary, there are some indications that systematic reviews, if not properly guided by important clinical questions, might amplify the unimportant issues and may result in a rather misleading scale of evidence to guide clinical decisions. Since most RCTs are performed by pharmaceutical companies, it is quite plausible that data-driven systematic reviews will reflect the priorities as perceived by pharmaceutical companies and not necessarily by the public and clinicians. Without a change in regulatory procedures, pharmaceutical companies will continue to pay little attention to comparative RCTs and will continue to assess drugs for indications which are worth the financial investment, neglecting rare but clinically important disorders [21].

Systematic reviews alone cannot fill the gap, and we urgently need primary research and high-quality and relevant clinical trials. In recent years, the problem has been acknowledged, and we have

seen the upsurge of initiatives in our discipline to develop independent clinical trial research networks [22–24] and, more recently, the promotion of an international federation of these networks to promote collaboration and to improve the quality and reporting of clinical research at an international level.

### Evidence-based medicine: where do we go from here?

An EBM approach should permeate medical education and inform academic medicine. Only if such a change is promoted can EBM become central to clinical practice and not trivialized to “cook-book” medicine. If EBM is successfully integrated into everyday practice it may become easier to conduct primary clinical research based on clinical needs rather than on commercial interests.

In primary research, more imaginative and effective research instruments are needed, and research strategies should be developed that take account of the peculiarities of dermatology compared with other disciplines. Qualitative research should not be neglected. It is the key to understanding what matters to patients, the intercultural variations in body image and how health needs for skin diseases are expressed and perceived in different situations.

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### Other useful resources

<http://www.ifdctn.org> (The International Federation of Dermatology Clinical Trials Networks).  
<http://www.ukdctn.org/> (The UK Dermatology Clinical Trials Network).

The chapter is partly based on Naldi L, Minelli C. Dermatology. In: Machin D, Day S, Green S, eds. *Textbook of Clinical Trials*. Hoboken, NJ: John Wiley & Sons, Inc., 2006.

## CHAPTER 2

# The rationale for evidence-based dermatology

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## What is evidence-based dermatology?

### Definitions

Sackett, a clinical epidemiologist and one of the founders of modern evidence-based medicine (EBM), defined the latter as “the conscientious, explicit and judicious use of current best evidence about the care of individual patients” [1].

Sackett’s definition is still one of the best, because it reflects a number of key concepts:

- “Conscientious” implies an *active* process that requires learning, doing, and reflection.
- “Explicit” implies that we can describe and replicate the *process* that is used to practice EBM.
- “Judicious” denotes the need for clinical judgment in applying evidence.
- “Current” implies being *up to date*.
- “Best” implies that we should seek the most *reliable* evidence source to inform practice.

As Chapter 18 elaborates, perhaps the most important and frequently forgotten phrase in this definition is “the care of individual patients.” The place for EBM is not in trying to score intellectual points in the literature or in humiliating colleagues at journal clubs; it is at the bedside or in the outpatient consulting room. As Chapter 75 emphasizes, EBM is a way of thinking and working, with improved health of patients as its central aim.

Nowadays, the term “evidence-based practice” is often used instead of EBM. The term “evidence-based practice” is a good phrase as it emphasizes the *doing* rather than *talking* about EBM, and may be defined as integrating one’s clinical expertise with the best external evidence from systematic research [2]. Evidence-based dermatology (EBD) simply implies the application of EBM principles to people with skin problems [3].

### What evidence-based dermatology is not

Despite the above clear definitions, the purpose of EBD is often misunderstood in the literature [4]. Some of these misinterpretations are shown in Box 2.1. First, EBD does not tell dermatologists what to do [1]. Even the best external evidence has limitations in informing the care of individual patients. To use R.E. Clerk’s meta-

phor, external evidence is just one leg of a three-legged stool – the other two being the clinician’s expertise and the patient’s values and preferences. Take one of those legs away, and the stool falls down. Clinical expertise and discussion of what matters most to patients in their choice of treatment options will always be at the heart of applying evidence during a dermatology consultation. EBD is not a cookbook of recipes to be followed slavishly, but an approach to medicine that is patient driven from its outset. Patients are the best sources for generating the important clinical questions, answers to which then need to be applied back to such patients [5].

Just as ordinary patients are at the heart of framing evidence-based questions, so too are ordinary clinical dermatologists at the heart of the practice of EBD [6]. EBD is not something that only an exclusive club of academics with statistical expertise can understand and practice, but rather it is something that all dermatologists can practice with appropriate training. Being able to critically appraise a published clinical trial or systematic review about a new dermatological treatment is a core competency that is as basic to being a dermatologist as the ability to examine, diagnose, or perform a skin biopsy.

Contrary to popular belief, the prime purpose of EBD is not to cut costs. Like any information source, selective use of evidence can be twisted to support different economic arguments. Thus, the relative lack of randomized clinical trial (RCT) evidence for the efficacy of methotrexate in psoriasis should not imply that methotrexate should not be used or purchased for patients with severe disease

#### Box 2.1 What evidence-based dermatology is not

- Something that ignores patients’ values.
- A promotion of a cookbook approach to medicine.
- An ivory-tower concept that can only be understood and practiced by an exclusive club of aficionados.
- A tool designed solely to cut costs.
- A reason for therapeutic nihilism in the absence of randomized controlled trials.
- The same as guidelines.
- A way of denigrating the value of clinical expertise.
- A restriction on clinical freedom, if this is defined as doing the best for one’s patients.

when there is so much other evidence and long-term clinical experience to support its use. But this is not to say that a clinical trial comparing methotrexate against other systemic agents, such as acitretin or fumarates, would not be desirable at some stage [7]. It was heartening, for example, to see a trial of a biologic for psoriasis compared against methotrexate as an active comparator [8], rather than the usual profusion of placebo-controlled studies that leave doctors confused about which treatment is best.

EBM should not be viewed as a restriction on clinical freedom, if clinical freedom is defined as the opportunity to do the best for your patients, as opposed to making the same mistakes with increasing confidence. Searching for relevant information for your patients frequently opens up *more* rather than fewer treatment options [9]. Shared decision-making through a physician–patient partnership is free to choose or discard the various options in whatever way gives the most desirable outcome.

Guidelines are not the same as EBM, although the two are frequently confused [10]. Guidelines may or may not be evidence based, but guidelines are just that – guidelines. Many dermatology guidelines now incorporate a grading system that describes the quality of evidence used to make recommendations and their strength [11]. Many guideline development groups use methods that combine the strength of available external evidence based on the hierarchy described more fully in Chapter 7 sometimes using specific criteria such as those as recommended by the Grading of Recommendations Assessment, Development and Evaluation working group [12], plus some method for suggesting whether a recommendation is a strong one such as the Strength of Recommendation Taxonomy system suggested by Ebell *et al.* [13]. Striking a balance between only recommending expensive new treatments based on high-quality placebo-controlled clinical trial evidence conducted by the pharmaceutical industry instead of other long-established treatments simply because they pass the “level A” evidence hurdle is a difficult one for guideline developers to get right [14].

## Problems with other sources of evidence

### Working things out on the basis of mechanism and logic

Many physicians base clinical decisions on an understanding of the etiology and pathophysiology of disease and logic [15,16]. This paradigm is problematic, because the accepted hypothesis for the etiology and pathogenesis of disease changes over time, and so the logically deduced treatments change too. For example, in the past 20 years, hypotheses about the etiology of psoriasis have shifted from a disorder of keratinocyte proliferation and homeostasis, to abnormal signaling of cyclic adenosine monophosphate, to aberrant arachidonic acid metabolism, to aberrant vitamin D metabolism, to the current favorite: a T-cell-mediated autoimmune disease. Each of these hypotheses led to logically deduced treatments. The efficacy of many of these treatments has been substantiated by rigorous RCTs, whereas other treatments are used even in the absence of systematically collected observations. We thus have many options for treating patients with severe psoriasis (for example, ultraviolet B, Goeckerman treatment, psoralen-ultraviolet A, methotrexate, ciclosporin, and at least six biologics) and mild to moderate psoriasis (for example, dithranol, topical corticosteroids, calcipotriol, and tazarotene). However, we do not know which is best, in what order they should be used, or in what combinations.

Treatments based on logical deduction from pathophysiology can have unexpected consequences. For example, the observation

that antiarrhythmic drugs could prevent abnormal ventricular depolarization after myocardial infarction logically led to their use to prevent sudden death after myocardial infarction. However, RCTs showed increased mortality in patients treated with antiarrhythmic drugs in comparison with placebo [17,18]. So, although patients' electrocardiograms looked a lot happier and smoother, more people died whilst on treatment. This example highlights the dangers of using surrogate outcome measures, such as electrocardiograms, for more meaningful outcomes, such as disability or death, simply because the surrogate measurements are easily made. The challenge with surrogate outcome measures is to ensure that they measure important things rather than trying to make measurable things important. Another classic example of the dangers in basing our treatments on empirical observations of “scientific” mechanisms is the clinical trial of thalidomide for toxic epidermal necrolysis (TEN) [19]. On the basis of observations that TEN is associated with high levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), a trial of thalidomide (a drug that inhibits the actions of TNF- $\alpha$ ) was commenced. The trial was stopped early because 10 out of 12 patients in the thalidomide group died, in comparison with three of 10 on placebo treatment. It was also found that those in the thalidomide group had an unexpected increase in TNF- $\alpha$  levels during treatment.

Some “designer” drugs, such as topical tazarotene, were promoted on the basis of their molecular mechanisms of action and may have appeared attractive at launch, but have been less exciting when tested in practice [5]. It might also be argued that the frequent narration of the superantigen story as a mechanism for antistaphylococcal treatments for atopic eczema is a smokescreen that obscures the real lack or uncertainty of evidence of clear benefit for such agents [20].

Given these lessons, many dermatologists have become less interested in *how* treatments work and are now daring to ask questions such as: “Does it work?” and – more important than a demonstration of statistically significant efficacy in comparison with placebo – “How *well* does it work in comparison with existing, more established treatments?”

### Personal experience

Although personal experience is an invaluable part of becoming a competent physician, the pitfalls of relying too heavily on personal experience have been widely documented [21–23]. These include:

- overemphasis on vivid, anecdotal occurrences and underemphasis on statistically significant strong evidence;
- bias in recognizing, remembering, and recalling evidence that supports preexisting knowledge structures (for example, ideas about disease etiology and pathogenesis) and parallel failure to recognize, remember, and recall evidence that is more valid but does not fit preexisting knowledge or beliefs;
- failure to characterize population data accurately because of ignorance of statistical principles – including sample size, sample selection bias, and regression to the mean;
- inability to detect and distinguish statistical association and causality;
- persistence of beliefs despite overwhelming contrary evidence [23].

Nisbett and Ross [24] provide examples of these pitfalls from controlled clinical research, and simple clinical examples abound. Physicians may remember patients assuming that those who did not return for follow-up improved, and conveniently forget the patients who did not improve. A patient treated with a given medi-



cation may develop a severe life-threatening reaction. On the basis of this single undesirable experience, the physician may avoid using that medication for many future patients, even though on average it may be more efficacious and less toxic than the alternative treatments that the physician chooses. Few physicians keep adequate, easily retrievable records to codify the results of treatments with a particular agent or of a particular disease, and even fewer actually carry out analyses. Few physicians make provisions for tracking those patients who are lost to follow-up. Thus, statements made about a physician's "clinical experience" may be biased. Finally, for many conditions, a single physician sees far too few patients to draw reasonably firm conclusions about the response to treatments. For example, suppose a physician who treated 20 patients with lichen planus with tretinoin found that 12 (60%) had an excellent response. The confidence interval for this response rate (i.e., the true response rate for this treatment in the larger population from which this physician's sample was obtained) ranges from 36% to 81%. Thus, the true response rate might well be substantially less (or more) than the physician concludes from personal experience [15,25]. Personal experience alone is also unlikely to pick up smaller treatment differences between active treatments. A new treatment must be substantially better than an existing treatment for a physician to notice. If, in the above example of lichen planus, standard treatment with topical corticosteroids resulted in a response rate of 55%, then the physician would need to treat 20 patients on average (number needed to treat equals the reciprocal of 60% minus 50%) to notice one additional success from tretinoin.

### Expert opinion

Expert opinion can be valuable, particularly for rare conditions in which the expert has the most experience or when other forms of evidence are not available. However, several studies have demonstrated that expert opinion often lags significantly behind conclusive evidence [21]. Experts suffer from relying on bench research, pathophysiology, and treatments based on logical deduction from pathophysiology, and from the same pitfalls noted for relying on personal experience [25]. Some have even questioned the value of content experts when producing systematic reviews of evidence [26].

Textbooks can be valuable, particularly for rare conditions and for conditions for which the evidence does not change rapidly over time. However, textbooks have several well-documented shortcomings. They tend to reflect the biases and shortcomings of the experts who write them. By virtue of the way in which they are written, produced, and distributed, most are at least 2 years out of date at the time of publication. Also, many textbook chapters are narrative reviews that do not consider the quality of the evidence reported [21,25,27].

### Uncontrolled data

Empirical, uncontrolled and unsystematically collected data form the basis of much of dermatology practice. This situation is justified by its advocates by two erroneous assumptions. The first is that it is acceptable to use such data because better evidence is not available – an assumption that is often not true due to lack of training in searching for relevant information, as discussed in Chapter 6. There is a surprisingly large body of high-quality evidence that is useful for the care of patients with skin disease, as exemplified by the growing body of evidence-based treatments discussed in this book and by the exponential increase in systematic reviews of skin treatments [28]. The second erroneous assumption is that the

majority of dermatologists already base their practice on the best evidence that is already available. The base of knowledge for the practice of medicine is expanding exponentially. It is estimated that, to keep up with the best evidence available, a general physician would have to examine 19 articles a day, 365 days a year [2]. Therefore, keeping up to date by reading the primary literature is now an impossible task for most practicing physicians [29]. The burden for dermatologists is no less daunting [5]. The challenge is to know how to find information efficiently, appraise it critically, and use it well. Knowing the best sources and methods for searching the literature allows a dermatologist to find the most current and most useful information in the most efficient manner, when it is needed. The techniques and skills needed to find, critically appraise, and use the best evidence available for the care of individual patients have been developed over two centuries. These techniques and skills are currently best known as EBM [2,15].

## The process of evidence-based dermatology

Having discussed the definition and rationale of EBD, how does one actually do it? This process is best considered in five steps (Box 2.2), although in real life they tend to merge and become iterative [5]. These steps are elaborated in subsequent chapters.

### Step 1: asking an answerable structured question

Developing a structured question that can be answered requires practice. An example of a useless question would be, "Are diets any good in eczema?" A better question, generated from a real clinical encounter, would be, "In children with established moderate to severe atopic dermatitis, how effective is a dairy-free diet in comparison with standard treatment in inducing and maintaining a remission?" Such a question includes four key elements:

- the patient population to which one wishes to generalize;
- the intervention;
- its comparator;
- the outcomes of interest and their timing that might make you change your practice [30].

Unless one uses such a PICO (patients, intervention, comparator and outcome) structure, it would be easy to waste time discussing and searching for data on the role of diets in preventing atopic disease, the effects of dietary supplements such as fish oil, studies that evaluate only short-term clinical signs, and those that deal with a "ragbag" of different types of eczema in adults and children. Bigby and Rzany discuss further examples of framing answerable questions in more detail in Chapter 5.

### Step 2: searching for the best external information

Publication of biomedical information has now expanded so much that it is hard to contemplate searching for relevant information without some form of electronic bibliographic search, followed by reading the original key papers. Most of us (including the authors)

#### Box 2.2 The five steps of practicing evidence-based dermatology

- 1 Asking an answerable structured question generated from a patient encounter.
- 2 Searching for valid external evidence.
- 3 Critically appraising that evidence for relevance and validity.
- 4 Applying the results of that appraisal of evidence back to the patient.
- 5 Recording the information for the future.

are not experts at performing complex electronic searches, and need to learn such skills. These skills are dealt with in more detail by Bigby and Corona in Chapter 6. As pointed out earlier, traditional expert reviews are risky, because often they have not been done systematically, and the links between the author's conclusions and the data are often unclear [31]. Thankfully, many systematic reviews have now been done in dermatology, and those that have been done in atopic dermatitis and acne have been mapped in a publically accessible resource at the Centre of Evidence-Based Dermatology (<http://www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/resources/index.aspx>). In the absence of good-quality systematic reviews, then, one often ends up searching for individual randomized controlled trials. Searching for trials on the Medline and Embase databases is hazardous unless one is proficient, because simply searching by the "clinical trials" type can miss up to half of the relevant trials due to coding problems [32]. The world's most comprehensive database of clinical trials is now the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) which can be found at <http://www.thecochranelibrary.com> and which contained 680 109 records in September 2012. Thankfully, it is also the easiest to search.

### Step 3: sifting information for relevance and quality

The usefulness of an article is a product of its clinical relevance, multiplied by its validity, divided by its accessibility [33]. Information sources need to be near the clinical area if they are to be used for patients. Becoming distracted by irrelevant but interesting citations is also a real hazard when reading search results. Two filters need to be applied if one is to keep practicing EBD: the first is to discard irrelevant information, and the second is to spend more time looking at a few high-quality papers. It is timely at this point to mention the concept of the hierarchy of evidence [34], which is discussed in more detail in Chapter 7. This means that if a randomized controlled trial is found that deals with the question of interest (for example, dietary exclusion in childhood atopic dermatitis), or better still a systematic review dealing with the same topic, one should critically appraise these sources rather than dilute what little time one has by reading lots of case series and case reports.

### Step 4: applying the evidence back to the patient

This is usually the most important step, although the least well developed in EBD. Key points to note here are:

- to consider how similar the patients in the studies are to the patient facing you now;
- whether the outcome measures used in those studies are clinically meaningful for both you as a practicing doctor and the patient;
- how large the treatment benefits were;
- what the drawbacks of the intervention were;
- how the evidence fits in with your patient's past experience and current preferences.

This difficult area is discussed in more detail in Chapter 18.

### Step 5: recording the information for the future

Having done so much work pursuing the above "evidence-based prescription" from question to patient, it might be useful to others and yourself to make a record of that information for future use as a critically appraised topic (CAT), although this has a limited

lifespan if not updated [2]. Such CATs could become the norm in dermatology journal clubs all over the world, replacing unstructured chats about articles selected for unclear reasons. Some dermatology journals have promoted the use of CATs as an educational tool [35,36].

The key point to remember about the process of EBD is that it *starts and ends with patients*. A problem highlighted during an encounter with a patient is the best generator of an EBM problem [37]. Even if one then searches and critically appraises the best data in the world, the utility of this exercise would be zero if it were not then applied back to that patient or other similar patients. Developing the skills to undertake evidence-based prescription requires practice.

Dermatologists will participate in the practice of EBD to different degrees depending on their enthusiasm, skills, time pressures, and interest [34]. Some will be "doers," implying that they undertake at least steps 1–4 highlighted in Box 2.2. Others will be more inclined to adopt a "using mode," relying on searching for secondary evidence sources such as evidence-based summaries – for example, systematic reviews that others have constructed – thereby skipping step 3, at least to some degree. Finally, some will incorporate evidence into their practice in a "replicating mode," following decisions of respected leaders (i.e., skipping steps 2 and 3). These categories bear some similarity to those of deduction, induction, and seduction that Sackett used to describe the methods that physicians employ to make decisions about therapy [21]. Such categories are not mutually exclusive, since even the most enthusiastic EBM practitioners in "doing" mode will flit to "user" and "replicating" mode according to whether they are dealing with a common or rare clinical problem.

## Conclusions

Few dermatologists would argue that their overarching professional role is to provide their patients with the best health care. To do so, a dermatologist must be able to assess the patient's physical condition, know the best and most current information about diagnosis, prevention, therapy, prognosis, and potential harm, and then apply that knowledge of universals to the individual patients [38,39]. Medicine is advancing very rapidly, creating major changes in the way we treat our patients. It is imperative that we, as health-care professionals, keep up with such changes. We need to be up to date with such new external evidence. We frequently fail to do this if we rely on passive means or an occasional flick through the main journals, and our knowledge gradually deteriorates with time. Attempts to overcome this deficiency by attending clinical education programs fail to improve our performance, whereas the practice of EBM has been shown to keep its practitioners up to date. EBM is a way of thinking that is intended to help accomplish these objectives. If we stick to thinking about *patients' welfare* when contemplating EBM, we are less likely to get things wrong [5,15].

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## CHAPTER 3

# The role of patient and public involvement in evidence-based dermatology

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### Introduction

Various terms are used to describe patients, carers, and members of the public involved in health care, particularly with regard to research. The term patient and public involvement (PPI) is now widely used, and we use it here. PPI means health professionals, patients, carers, and the public working together to improve the health of the communities they represent.

Compelling evidence shows that patients who take an active part in managing their own health care have better outcomes than those who are passive recipients. Increasingly, patients are active, informed people who want to know more about their condition and have more control over their own care. Education can help patients share responsibility for their own care. They also need access to trustworthy information to make important choices about their treatment. Easy access to relevant, evidence-based information will help them to choose the care they need and want.

Those involved in PPI in evidence-based dermatology are bringing their experience and perspective to the table. Their participation in activities such as the prioritization of research projects, through to proof reading of articles for public consumption will help to ensure that any work done is of interest and of use to all end users.

### The many benefits and roles of patient and public involvement in health care

PPI can bring many benefits to health care, not least having better informed patients and carers as outlined above. Other benefits include improving the quality of health care and making better use of existing resources; this includes improving access to services and making monitoring and evaluation of services more effective.

The roles of PPI in health care are many and varied and are outlined below (several are discussed in more detail later):

- playing an active part in self care as far as possible;
- working with professionals to improve one's own care and that of other family members and those in the general community;
- to share personal experiences of living with a disease and to inform and educate other patients and professionals;
- assisting with the development and governance of health institutions and organizations;

- contributing to research policy and practice by helping to decide research priorities and funding and helping to improve the design of research;
- to support the recruitment of patients into research studies;
- helping to disseminate important research findings.

Such PPI can benefit all those involved in the health-care process in different ways. For example, patients will benefit from seeing their views considered and used to improve the quality of care for others, while health service managers will benefit from improved standards of more patient-friendly services. Health service researchers can benefit greatly, as working with patients, carers, and the public from the very start of their projects can much improve the quality of their research design and outputs.

### The skin shows: it matters psychologically and socially

The roles of PPI in health care are generic across all clinical specialties. Skin diseases differ from other illnesses in being much more visible, whether through constant itching, visible patches on the skin, or flaking of the skin. In this crucial area, patients and carers can help professionals understand and learn what matters to people with various skin conditions; those unaffected may find these aspects difficult to understand and recognize appropriately.

Many people with skin disease experience significant psychological and social distress such as depression and fear of stigma [1]. A recent German study of patients with occupational hand eczema found a high prevalence of anxiety and depression among them [2]. Although recognized, this has rarely been addressed when considering treatment options, and a survey [3], conducted for the European Commission on public opinions, found that the patients they surveyed felt "doctors do not take account of the 'psychological' impact of treatments and their effects in day-to-day life."

The extent of disease may not be the most important factor in considering a patient's suffering. Self-esteem, self-image, the site of the lesions, how far the patient feels disabled, and the support networks available should all be considered. For example, an office worker may tolerate extensive psoriasis on covered areas of the body, but as soon as the psoriasis starts to affect "high expression" and visible areas, such as the face and hands, quality of life can drop drastically. More could be done to ensure that practitioners assess

the impact of psychosocial issues, and that treatment provided is just one part of the holistic management of skin disease. A study of core beliefs and psychological distress in patients with psoriasis and atopic eczema attending secondary care identified a potential link between early maladaptive schemas (vulnerability to harm and defectiveness) and anxiety, social isolation and depression [4]. Such findings have clinical implications for the psychological management of such patients. Although a Cochrane review of psychological and educational interventions for atopic eczema in children found little research in the area, relaxation methods appeared to reduce the severity of childhood eczema, as did several health education programs for the families of affected children [5]. Skin camouflage is an important treatment option for certain skin diseases (e.g., vitiligo). The British Association of Skin Camouflage (<http://www.skin-camouflage.net/>) provides advice on skin camouflage and states, “The psychological benefit to people who have been shown how to successfully apply and manage skin camouflage cannot be over-emphasised . . . it empowers them to face the world, with confidence!”

## Education and information for self-care

### The role of patient support groups

Treatment of a skin disorder involves more than a professional diagnosis, the use of medication (prescription or over-the-counter remedies), or even care in hospital. Those affected may seek advice from a clinician but also rely on support from family members, friends, and fellow patients to help manage their condition. Many will seek further information outside the clinical community to educate themselves about the management of their skin disease, and patient support groups (PSGs) can be an excellent resource for this.

PSGs provide a setting in which people who share similar experiences come together to offer reciprocal and mutually helpful practical and emotional support. People go to a PSG for many different reasons; some simply want information and will then move on. Others may want to make sense of what is happening to them by sharing with those who have been through something similar. Often, advice from a PSG can resolve practical everyday problems that clinicians are not aware of or avoid dealing with due to embarrassment or a lack of understanding. Dermatology PSGs and advocacy groups are increasingly being recognized as important in health policy, patient education, national guideline committees, and research [6].

The British Association of Dermatologists’ website (<http://www.bad.org.uk/site/575/default.aspx>) [] lists over 60 PSGs in the UK for both common and rare skin conditions. The groups are generally run by patients or non-health-professionals, often volunteers. Many have been founded by patients and/or carers affected by the condition concerned who have been frustrated by the lack of available information. PSGs support patients living with their diagnosis through information leaflets (often produced together with professionals), newsletters, confidential phone lines, personal email responses, and information on websites. Leaflets and information sheets are often tailored to specific groups (e.g., children, parents, teachers, general public), but groups also often give health professionals valuable information. PSGs are found across the globe; for example, in Canada, The Canadian Skin Patient Alliance is an overarching nonprofit organization providing education, information, a supportive on-line community, and opportunities to create and join local support groups for people with skin disease (<http://www.skinpatientalliance.ca>).

Such information is essential for patients. A person living with a long-term condition spends on average 3 h per year with a clinician; the rest of the time they are in charge of their own care [7]. Informing and educating patients and carers, helping them interpret research evidence, and correcting misconceptions can help with improved self-care and shared decision-making [8]. In this way, PPI can thus help not only patients and carers but also health providers, since self-care at home can reduce attendance at specialist clinics.

### The rise of internet and social networking

Skin conditions can limit the opportunities that patients or carers have to interact in the outside world – for example fewer mothers of children with atopic eczema have an outside job [9]. The virtual world can enable the person to reach out to address their concerns at a time to suit them. Dermatology patients may seek more internet advice than patients affected by other disorders; the reasons include frustration with explanations received from professionals, feelings of helplessness, desire for anonymity, coping with feeling ill-informed, and seeking information for another [10].

As noted, most PSGs have website and contact emails, but in the past few years much more has been added. Social networking includes news, blogs, podcasts, virtual communities, twitter, wikipedia, videos, mobile phone apps, and other things like photo sharing through web-based technologies. Not only PSGs offer relevant information; third-sector, government, and pharmaceutical organisations all have resources for the patient, carer, and the health professional. It is perhaps worth mentioning that not all websites that appear to provide neutral medical information are in fact doing so. Some are funded by for-profit companies wishing to highlight their products, so it is worth looking carefully at who is running and funding the information being provided. Different search engines generate different results, sending the user to different sites [11]. Social networking allows contact with like-minded people both nationally and internationally. Each different web-based medium gives different opportunities to interact with people concerned with dermatology, potentially promoting health literacy, which should strengthen patient engagement [12].

Excellent examples of websites showing patients’ experiences are Healthtalkonline (<http://www.healthtalkonline.org>) and the sister website Youthhealthtalk (<http://www.youthhealthtalk.org>). Here, one can share in over 2000 peoples’ experiences of over 70 health-related conditions and illnesses. Unfortunately it doesn’t yet include experiences of skin disease, but Youthhealthtalk sections on acne, psoriasis, alopecia and eczema in young people are planned for 2015/16 (available at: [www.Youthhealthtalk.org](http://www.Youthhealthtalk.org)). A section on participating in clinical research may be of general interest.

It has been shown that a great deal of medical information on the web is wrong [13], due to carelessness, misinterpretation, misrepresentation, or inappropriateness. While primary care physicians seem more likely to seek answers to clinical questions from colleagues than from electronic sources [14], less is known about patients’ hierarchy of information. The acquisition of poor-quality information alone may not empower patients to share decision making [15] and may even result in “cyberchondria.”

Individual voices can blur boundaries. Health professionals, patients, and carers can connect and participate in real-time topical discussions (for example, thorough Twitter). But individual voices can be persuasive and misleading – it is generally unwise to rely on other people’s stories as a guide to how likely you are to experience similar benefits or harms from an intervention.

## Patient and public involvement in the research process

There are many opportunities for PPI in research, including assisting with Cochrane systematic reviews, helping to identify research priorities, peer reviewing applications and proposals, commenting on patient-relevant outcomes in research, helping to develop study documents, and the dissemination of research results. In health research, PPI is crucial as it helps to ensure that the research undertaken is useful and relevant to patients [16]. In the UK, INVOLVE (<http://www.invo.org.uk>) was established in 1996 and is now part of, and funded by, the National Institute for Health Research (NIHR), to support active public involvement in National Health Service, public health, and social care research. It aims to bring together expertise, insight, and experience in the field of public involvement in research, to advance PPI as an essential part of the research process. INVOLVE is one of the few government-funded programs of its kind in the world and is an excellent starting point for finding out more about the role of PPI in research.

An example of PPI in dermatology research has been the establishment with NIHR funding of a Patient Panel in 2009 by the Centre of Evidence Based Dermatology at the University of Nottingham, UK (<http://www.nottingham.ac.uk/dermatology>). It aims to create a more effective research environment and to give more support for those wanting to get involved in dermatology research by holding regular training events. The panel has over 20 active members involved in a wide range of research activities.

## The role of patient support groups

As well as providing information and advice, many dermatology PSGs further support PPI by directly funding research, supporting participation in research, or both. In the UK, the sums awarded by dermatology PSGs for research funding are modest compared with other disease areas. Over the past 40 years the Psoriasis Association (<http://www.psoriasis-association.org.uk>) has awarded over £4 million in research funding and is now focusing on funding the next generation of researchers through PhD projects. DEBRA (<http://www.debra.org.uk>), the UK charity working on behalf of people with the genetic skin blistering condition epidermolysis bullosa, funds research into the possible causes and treatments of the disease. In addition, the umbrella group DEBRA International (<http://www.debra-international.org>) helps to coordinate the research activities of over 30 member organisations across the world. In the USA, the National Eczema Association (<http://www.nationaleczema.org>) gives small grants for patient-orientated eczema research. These focus on topics of primary importance to the patients and their families: itch, infection, prevention, skin-barrier function, and psychosocial aspects of the disease.

A number of PSGs promote research studies on their websites and in newsletters to help raise the profile of such studies to potential participants in addition to helping to disseminate research results. In the UK, the National Eczema Society (<http://www.eczema.org>) and the Vitiligo Society (<http://www.vitigosociety.org.uk>) were partners in the priority setting partnerships outlined below which helped identify the top clinical research priorities for these disorders.

## Cochrane systematic reviews

The Cochrane Collaboration (<http://www.cochrane.org>) actively promotes PPI in its work, and the Cochrane Consumer Network (CCNet) was set up in 1995 to help manage this aspect (<http://consumers.cochrane.org>). The Cochrane Collaboration is divided

into Cochrane review groups responsible for particular disease areas. The Cochrane Collaboration strongly encourages PPI in their protocols and reviews, and many groups liaise with CCNet to do this.

A patient and carer perspective on systematic reviews is important. Most lead review authors are health professionals and consider a question for a review because of their own experiences in a clinical environment or through health-care research. The purpose of PPI input during the review process is to:

- ensure that a review question is relevant to people requiring health care;
- identify outcomes from health-care interventions that matter to patients – these may differ from those identified by service providers;
- improve access to reviews by ensuring that the review can be read and understood by a wide audience and that language is sensitive to patients, carers, and the public;
- weigh the benefits of a health-care intervention against the potential harms – only patients can say which issues matter most to themselves and their families or carers;
- help decide priorities for new reviews.

Members of CCNet are individuals as well as community-based organizations from across the world. CCNet supports and trains its members, encouraging them to join in the work of the collaboration. It works to keep consumers informed, develops training materials, helps demystify scientific jargon to make reviews more accessible to the public, and publishes a digest of new additions to the Cochrane Library, including full lay summaries of reviews. The CCNet website is a means of commenting on issues and reviews and links to other sources of evidence-based health care. In addition, some groups like the Cochrane Skin Group (<http://skin.cochrane.org>) have set up their own list of consumers who have previously commented or have expressed an interest in a particular area. An outstanding example of PPI in Cochrane Skin Group reviews can be found in the treatments for vitiligo review and update, led by a vitiligo patient, Maxine Whitton [17].

## Priority setting partnerships

Priority setting partnerships bring patients, carers, and health professionals together with the aim of identifying shared priorities for research on specific health problems. In the UK, this is facilitated by the James Lind Alliance (JLA) which supports and guides the priority setting partnership as a neutral facilitator (<http://www.lindalliance.org>). The aim is to agree by consensus on a top 10 list of uncertainties for future research. This approach leads to priorities that reflect both clinical and patient perspectives and, therefore, should yield the greatest improvements in health care. An online guidebook (<http://www.jlaguidebook.org>) helps those who wish to carry out a priority setting partnership. These questions are then published in the Database of Uncertainties about the Effects of Treatments (DUETs, <http://www.library.nhs.uk/duets>) to prompt research funders and commissioners. Priority setting partnerships have been working on a variety of disorders, including asthma, type 1 diabetes, and schizophrenia. To date, two partnerships have worked in dermatology: one on vitiligo [18] and one on eczema treatments.

## Vitiligo Priority Setting Partnership

A recently updated Cochrane systematic review “Interventions for vitiligo” showed that the research evidence for the treatment of vitiligo was poor, making it difficult to make firm recommendations



for practice [17]. The Vitiligo Priority Setting Partnership was established and included patients, representatives from the Vitiligo Society, health professionals, and researchers. It worked with guidance from the JLA as outlined above with the aim of finding out why there was so little high quality research on the treatment of vitiligo. The priority setting partnership worked in three phases: a survey to collect the treatment uncertainties from patients and health professionals; a ranking exercise in which participants were asked to vote for their favorite topics from a list of the most frequently asked uncertainties; and finally, a workshop at which the most popular treatment uncertainties were developed into research questions [18].

The final list of the top 10 treatment uncertainties included interventions such as systemic immunosuppressants, topical treatments, light therapy, and the impact of psychological interventions on the quality of life of patients with vitiligo. Five research vignettes based on these top 10 uncertainties were submitted to the NIHR Health Technology Assessment Programme, which has since called for a randomized controlled trial of the use of UVB light combined with topical corticosteroid for the treatment of vitiligo.

### **Eczema treatments priority setting partnership**

Though much research has been done on eczema, no explicit attempt had been made to identify the treatment uncertainties in eczema that matter to patients, their carers, and the professionals treating them. A priority setting partnership for eczema treatments did this. As with the Vitiligo Priority Setting Partnership, the Eczema Priority Setting Partnership worked in three phases. The final workshop used the ranked uncertainties, current evidence, and personal/professional experience to develop research questions about eczema treatments which will be published, publicized, and used to guide future research as was done for vitiligo.

### **Clinical trials: development, delivery, and dissemination**

PPI is crucial not only to the design and conduct of a clinical trial but also to the dissemination of study results. Although currently recognized as being important, a recent study by the Medical Research Council (MRC) revealed that between 1989 and 2009 only 31% of MRC funded trials had some form of PPI [19]. In the UK it is important to remember that now many funders of clinical research, including NIHR funding bodies, will only fund applications that demonstrate meaningful PPI throughout the planned study.

### **Patient and public involvement in clinical trial development**

Involving patients and carers from the early stages of the research development process helps ensure that the question posed by the study is relevant to those who would be involved. This should help recruitment into the trial, as patients will be more interested in taking part. Such input can make sure that the number, timing, and duration of visits required for a study are acceptable to patients and carers, along with the treatments/interventions planned. In addition, PPI can help identify study outcomes important to patients which the professionals may not have considered. This is well demonstrated by the STOP GAP study of pyoderma gangrenosum, where, after focus groups and structured interviews with patients, pain control was given greater prominence as an outcome measure for the trial [20]. Further involvement in the design and wording of relevant study materials, such as patient information sheets and

diaries, will make sure that such documents are clear and easy to understand.

### **Patient and public involvement in clinical trial performance**

An obvious role for PPI in the performance of clinical trials is for patient representation on a trial steering or management committee to see that the needs of the study participants are being considered throughout the duration of the trial. People can also be involved by using previous study participants to act as patient advocates, encouraging their engagement to take part in a trial. PSGs can help recruitment by advertising on their websites and social networking. The Dermatological Sciences Research Group at the University of Manchester, UK, has a significant online presence to boost recruitment strategies. It uses Facebook (<https://www.facebook.com/pages/Manchester-Skin-Research/197339573612685>) and Twitter (@McrSkinResearch) to highlight studies that are actively recruiting and to keep participants and potential participants informed on their progress and their research.

### **Patient and public involvement in disseminating clinical trial results**

Results from clinical research are published in scientific and medical journals that mostly do not reach the public and are hard for lay readers to understand. This can make the results of clinical research inaccessible for the very people they aim to benefit. The purpose of PPI in helping to disseminate research results is to give advice as to how and when research results should be disseminated, to help widen the audience for the dissemination of clinical research results, and to identify existing research that is not currently being disseminated or implemented. This can be done not only by helping to draft accessible reports and lay summaries of research findings, but also by suggesting different ways in which research results can be presented and distributed so that they are accessible to people of all age ranges and hard-to-reach groups (e.g., podcasts and video clips). Becoming an advocate of research in the patient community and communicating results via relevant PSG websites and social networking groups is becoming an important way of disseminating study results to patients, carers, and the public.

### **Summary**

Given that many skin conditions are chronic, a high proportion of patients and their carers want to know as much as possible about their skin disease; not only the causes and prognosis for their disorder, but also the costs and benefits of the many treatment options available to them. Health professionals, patients, and carers have many opportunities to work together to benefit the field of evidence-based dermatology, and PPI is increasingly recognized as a vital component of successful skin research.

Patients and carers are often in the best position to guide researchers and health professionals on what matters to them most in terms of therapeutic benefit and can give psychological support and useful information to fellow patients and carers in ways that doctors cannot. They are well placed to help prioritize relevant dermatology research by framing research questions that are the most important to them and by helping researchers choose meaningful outcome measures for such studies. PSGs should not be ignored in research; they are ideally positioned to help boost recruitment by advertising studies, assist with the dissemination of study results, and, of course, fund research projects.

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## CHAPTER 4

# The Cochrane Skin Group

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### Background

The Cochrane Collaboration developed in response to a challenge issued by Archie Cochrane (1909–1988), a British epidemiologist, who in 1972 pointed out the deficiencies of reviews of the medical literature and the lack of access to up-to-date information about health care [1]. In response to his criticism about the great ignorance of the effects of health care, the international organization The Cochrane Collaboration was set up in 1993 at a meeting of 77 people from 11 countries, after the first Cochrane Centre had opened in 1992.

Archie Cochrane wrote [2]:

It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials.

The Cochrane Collaboration aims to facilitate systematic assessment of the available evidence from clinical trials in the form of systematic reviews, for the benefit of both health professionals and the general public. Reviews are now published in *The Cochrane Library* (<http://www.thecochranelibrary.com/>) electronically via a website. This is free to access for many people through a national provision license, such as is provided by the British National Health Service (NHS) and in low-income and middle-income countries through various initiatives to allow access (<http://www.thecochranelibrary.com/view/0/FreeAccess.html>).

The year 2014 is The Cochrane Collaboration's 22nd year. It has grown to be an organization in which more than 31 000 people from over 120 countries contribute, but the 10 guiding principles of The Cochrane Collaboration remain unchanged:

- collaboration
- building on the enthusiasm of individuals
- avoiding duplication
- minimizing bias
- keeping up to date
- striving for relevance
- promoting access

- ensuring quality
- continuity
- enabling wide participation.

### The Cochrane Skin Group

The Cochrane Skin Group (CSG) is a network of people from all over the world committed to producing and updating systematic reviews of trials relating to skin conditions. Members of the CSG are linked together by us at the editorial base, and we are keen to harness the energy and expertise of individuals whether they are from a clinical, scientific, or lay background. From the very beginning, consumer involvement has been prominent, and the CSG has become truly international and multi-disciplinary. Over 600 CSG authors are now supported worldwide.

The CSG editorial base was registered as a Cochrane entity in December 1997, and it is one of the 53 review groups that make up The Cochrane Collaboration. The founder, Professor Hywel Williams, is the coordinating editor of the group, which has its editorial base at the University of Nottingham, UK.

In addition to the coordinating editor, the editorial base also includes a managing editor, a trials search coordinator, and an editorial assistant. The CSG is supported by 10 key editors, 2 statistical editors, 2 methodological editors, and a feedback editor. The details and contact information for these editors can be found on the CSG website (<http://skin.cochrane.org/contact-editorial-team>).

Infrastructure support for the editorial base comes from the National Health Service Research & Development Programme, in the form of a National Institute for Health Research (NIHR) Cochrane Review Group Infrastructure Award, which runs for 5 years until 2015. The group accepts no funding from pharmaceutical companies. All our editors publicly declare their interests on our website.

Our systematic reviews benefit dermatology by providing the evidence on which dermatologists and other health professionals can base their clinical decisions, and by helping people with skin diseases become more informed about their health care.

Traditionally, Cochrane systematic reviews have differed from other systematic reviews in important ways: the authors have openly declared their intentions in the form of a peer-reviewed published protocol; the review has been written by several people, each bringing a unique contribution to the team; the search for randomized controlled trials (RCTs) has been wide (i.e., it has not been confined to one or two databases), and the author team has pledged to update the review regularly so that it is always providing the best available evidence for health care.

The quality of Cochrane reviews depends on whether the authors have drawn their conclusions from a valid assessment of the studies they have included in their review. They do this by assessing the biases of each study using The Cochrane Collaboration's "Risk of bias" tool, which is described in the *Cochrane Handbook for Systematic Reviews of Interventions* [3]. Working at the editorial base we get great satisfaction from helping authors produce quality reviews. To that end we welcome the recent introduction of the Methodological Expectations of Cochrane Intervention Reviews document, which gives the standards to which we should all adhere for the conduct and reporting of new Cochrane reviews.

Being part of a Cochrane review can be a challenging but also a great learning experience for all involved; most authors are volunteers. Some author teams have great fun and form lasting friendships both with each other and us back at the editorial office. Also, leading a review team may have definite career benefits. Public authorities in some countries give grants for particularly important topics to pay a member of the review team for time dedicated to the review.

### Types of Cochrane reviews

The Cochrane Collaboration has traditionally produced "intervention" reviews which assess RCTs addressing a particular clinical question. However, it is recognized that RCTs are not always appropriate for answering some questions, and so non-randomized studies may have to be included. As these studies tend to be more biased, the means to deal with them must be specified in the protocol. In recent years, diagnostic test accuracy reviews have been published; the CSG is now preparing a protocol for such a review. Cochrane overviews are those which bring together a number of small intervention reviews rather than the primary studies. The CSG generally aims to write large "all-encompassing" reviews of primary studies because we think these are of more use to the practitioner and to the person who has the particular skin condition; therefore, we have less need to write "overviews of reviews." Finally, Cochrane methodology reviews address methodological issues.

### Scope of the Cochrane Skin Group

Around 1000 skin diseases are described in the Topic List on our website [4]. These are based on the British Association of Dermatologists' diagnostic index and are used to classify our reviews. As well as standard medications and interventions for skin diseases, we also include cosmetic skin care products, alternative or complementary treatments, and medications that may be prescription drugs in one country and over-the-counter preparations in another. There is inevitably overlap with other Cochrane Groups, particularly with Wounds, Sexually Transmitted Infections, Pain and Palliative Care, and Infectious Diseases, so those with an interest in dermatology should also look for relevant reviews produced by other groups.

## Editorial process: join the Cochrane Skin Group and publish a high-impact paper!

For those keen to contribute to the development of a CSG systematic review, the process begins with individuals getting together with an important clinical question, which they may have suggested themselves or seen advertised on the CSG's website [5]. The team of authors on a review will ideally include a lead author who will assign tasks to the team and ensure they keep to the time-lines for completion; this person will of necessity devote much of their time to the review and will need at least one other person on the team to commit time to independent data extraction and generally to help complete the review. The other team members may not need to commit so much of their time, but will include:

- an experienced Cochrane author who can guide the team in the process;
- a clinician who is an authority on the subject of the review;
- a methodologist or statistician who will guide the team in understanding the results and doing the analyses; and
- a consumer who will aim to ensure the review is understood by the intelligent layman, that it adequately reflects the experience and social impact of the disease on the individual and family, and addresses outcomes in a way that is important to a person with the skin condition or caring for someone with that skin condition.

As Cochrane reviews are published in English, we ask that someone on the team has a good command of written English. Once the team of authors is formed, a title has to be registered. When it is accepted the authors are officially given access to the title through the Cochrane Information Management System, known as "Archie." First, the team must publish a protocol: the plan for the review. This will include a background section, a search strategy, and the planned methods for study selection, data extraction, and analysis.

Within 2.5 years of title registration, a review should be completed and published. The main stages of writing a Cochrane review are that:

- 1 a full and systematic search is undertaken;
- 2 relevant papers and other information are gathered;
- 3 two authors independently decide which papers meet the inclusion criteria;
- 4 these papers are then evaluated in a "Risk of bias" assessment;
- 5 the data are extracted and critically analyzed – with a meta-analysis if appropriate; and
- 6 the data are summarized and conclusions drawn in a way that health practitioners, managers, and consumers can understand.

Authors are expected to update their reviews at least every 2 years.

Each review is prepared in a defined manner to ensure consistency and high quality, using The Cochrane Collaboration's own free software, "Review Manager." Both the protocol and review undergo peer review by an editor, an external content expert, the statistical and methodological editors, and at least one consumer. Necessary revisions must be made by the authors and accepted by the editorial team before publication in *The Cochrane Library*.

### Support offered by the Cochrane Skin Group editorial base

The CSG aims to provide worldwide support at the end of an email. When emails get too complicated we are happy to speak by tele-



phone. We will help you create a team. For example, if you as the lead author cannot find team members with the skills you need, our editorial assistant will do all she can by writing to the membership seeking additional co-authors for you.

Upon officially becoming an author, we disseminate a range of documents on a variety of review processes, we highlight available review courses, give tips on avoiding plagiarism, share useful web links (including access to Cochrane's unique online training resources), and provide a guide to the review software. We also offer help with the translation of papers.

If a team is really struggling to complete its review, we will in some cases pay for a freelance systematic reviewer to work with it to offer expert guidance.

## Responsibilities of Cochrane Skin Group author teams

The editorial base expects that a title will be developed into a protocol within 6 months of its registration, and a review will be submitted for consideration for peer review within 15 months of the protocol being published in *The Cochrane Library*. During the title registration process, we ask new teams to sign an Author Agreement confirming their acceptance of these terms.

We ask authors to submit their protocols or reviews in as good a condition as possible to the editorial base. To help achieve this standard, the managing editor will work through the submission and ask you to amend any omissions or errors before it goes to the coordinating editor. Authors can expect the CSG to process protocols from their acceptance at the editorial base to submission to *The Cochrane Library* within 3 months; for reviews this period is 6 months. But the time taken is greatly influenced by how rapidly all the referees reply and how long the authors take to respond to the referees' comments.

To adhere to these timelines, authors are expected to respond to the referees' comments no longer than 1 month or 2 months, for protocols and reviews respectively, after they originally received them. The CSG reserves the right to de-register titles if deadlines are not met. However, we aim to help rather than penalize author teams, and we do all we can to assist and only reluctantly withdraw publications and readvertise for new teams.

## How do review teams find trials?

Review teams work closely with our trials search coordinator (TSC) to identify RCTs for inclusion in their reviews. When a team is working on a protocol, the TSC will work with them to develop a draft search strategy for their topic for MEDLINE, and will advise on which databases and other sources it would be appropriate to search. The TSC uses the draft search strategy as a basis for developing strategies for other databases once the protocol is published and the team is working on the review proper.

The CSG currently advises that in collaboration with the group's TSC, review authors search the following databases as a minimum:

- the Cochrane Skin Group Specialized Register (see below);
- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*;
- MEDLINE or PubMed;
- EMBASE (a biomedical database that has a particularly comprehensive coverage of pharmacology, drug research and toxicology);
- LILACS (Latin American and Caribbean Health Science Information database).

In addition, we encourage review teams to search the following trials registers to identify trials that may not yet have published reports:

- the metaRegister of Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com));
- the US National Institutes of Health Ongoing Trials Register ([www.clinicaltrials.gov](http://www.clinicaltrials.gov));
- the Australian New Zealand Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au));
- the World Health Organization International Clinical Trials Registry platform ([www.who.int/trialsearch](http://www.who.int/trialsearch));
- the EU Clinical Trials Register ([www.clinicaltrialsregister.eu/](http://www.clinicaltrialsregister.eu/)).

Teams may also want to search other web-based sources or databases, particularly subject-specific or non-English language resources. They may also wish to hand-search journals or conference proceedings (hand-searching refers to the process of manually checking a physical copy of a journal or conference proceedings by eye) or explore the "grey literature" in order to find additional reports of trials relevant to their review topic. More information on the CSG's searching methods is available [6].

## The Cochrane Skin Group Specialized Register

One of the key resources available to review teams searching for trials is the CSG's Specialized Register, a register of over 9000 (June 2012) reports of controlled trials in dermatology. It contains reports of both RCTs and controlled clinical trials (CCTs) identified by a combination of hand-searching and database searching by the CSG, and is a valuable resource for those preparing systematic reviews on dermatology topics. The Specialized Register is also used to feed new trials into the Central Register of Controlled Trials, part of *The Cochrane Library*.

## The Cochrane Library

The electronic *Cochrane Library* is the main product of the Cochrane Collaboration, and is the place where you will find all our published protocols and reviews.

*The Cochrane Library* (<http://www.thecochranelibrary.com/>) is a collection of seven databases and is the single best source of reliable evidence about the effects of health-care interventions. The databases are as follows:

- The Cochrane Database of Systematic Reviews (CDSR), which contains protocols and reviews prepared and maintained by Cochrane review groups.
- CENTRAL, which contains bibliographic information on controlled trials, including reports from conference proceedings and many other sources not listed in other bibliographic databases.
- The Cochrane Methodology Register (CMR), a bibliography of publications that report on methods used in the conduct of controlled trials.
- The Database of Abstracts of Reviews of Effectiveness (DARE), produced by the Centre for Reviews and Dissemination in England, which contains critical assessments and structured abstracts of other high-quality systematic reviews.
- The Health Technology Assessment (HTA) Database, which brings together details of completed and ongoing health technology assessments (studies of the medical, social, ethical, and economic implications of health-care interventions) from around the world. The HTA database is produced by the Centre for Reviews and Dissemination in England.

- The NHS Economic Evaluation Database, a register of economic evaluations of health-care interventions.
  - About The Cochrane Collaboration database. This database contains information on the 80 groups (Issue 6, 2012) that make up The Cochrane Collaboration.
- CDSR, CENTRAL and About are published monthly. DARE, CMR, HTA and EED are published quarterly.

## The role of consumers

“Consumers,” rather than “patients,” is the term given to people who have the skin disease that is the subject of the review or care for someone with that condition. Participation of consumers in reviews as co-authors, in some cases lead authors, and as referees has always been very important to the CSG. Consumers can help a team clearly describe the social impact of the condition, and define the ultimate aim or question that they are trying to answer in their review; they help to ensure the review is understood by the intelligent layman, and in particular they contribute to the 400-word précis of the review that is the plain language summary.

Where possible, we encourage two or more consumers to work together to produce a combined set of comments on a protocol or review. This is especially valuable when it reflects different geo-economic perspectives.

Following on from their importance to Cochrane and the Cochrane Consumer Network, within the wider department of the Centre of Evidence Based Dermatology in Nottingham, of which the CSG is a part, consumers have contributed notably through the Patient Panel in the development and design of RCTs by the UK Dermatology Clinical Trials Network.

## Impact of our reviews

Cochrane reviews have an impact on the wider community through the reviews themselves and their reputation for quality; through serving to teach about the principles of evidence-based medicine; through products of the review being presented in different ways for different audiences; through different media; through the results being used by various public bodies; and through authors using their Cochrane reviews to apply for grants for research proposals. The Impact Factor is a tool for ranking, evaluating, and comparing journals and is a measure of the frequency with which the “average article” in a journal has been cited in a particular year. The CDSR is ranked in the top 10 out of the 153 journals in the “Medicine, General & Internal” category: the 2011 Impact Factor was 5.9. The impact for CSG reviews in 2010 and 2011 was comparable to the highest rated dermatology journal: the *Journal of Investigative Dermatology*.

## Communicating with different audiences

The plain language summaries, podcasts, and videos aim to reach a wide audience with a succinct message about the core findings of the review.

The structured abstract and the authors’ conclusions highlighting their implications for research and for practice reach those who wish to understand a little more of the subject of the review, and the Cochrane Journal Club aims to promote discussion of reviews within a clinical department.

The full reviews, some of which can be huge documents, are generally only read in their entirety by those with a particular interest in that subject, by professional guideline writers or by those

involved with developing health policies. They can inform and improve health-care decision-making by advising on the design of future clinical trials; for example, in vitiligo [7,8] and in the management of atopic eczema [9,10]; see also the CREAM study at <http://www.controlled-trials.com/ISRCTN96705420/> (N. Francis, unpublished results, 2014).

They can inform guidelines used for setting health policies; for example, minocycline for acne [11,12], topical treatments for chronic plaque psoriasis [13,14], and safety of topical corticosteroids in pregnancy [15,16]. Reviews may also lead to derivative articles [17].

In terms of research commissioning and priority setting, our review on “Interventions for preventing occupational irritant hand dermatitis” [18] has also led to an HTA call for a clinical trial in health-care workers to address uncertainties ([http://www.hta.ac.uk/funding/Outcomestableweb\\_Apr12.pdf](http://www.hta.ac.uk/funding/Outcomestableweb_Apr12.pdf)).

Following The Cochrane Collaboration’s acceptance as a non-governmental organization in official relations with the World Health Organization, the Department of HIV/AIDS at the World Health Organization asked the CSG to assist with guidelines they are writing for treating the skin conditions developed by people with HIV. The CSG supported this work by reviewing the department’s search strategy for finding evidence-based material to support the guidelines.

## Co-publication

The CSG is keen to encourage authors to consider the life their Cochrane reviews will have after publication. We ask authors at the title registration stage to consider publication of summary articles of their reviews to widen dissemination of their findings. The Cochrane review should be published either before or at the same time as the publication in another journal. The CSG has co-publication agreements with the *Journal of the American Academy of Dermatology* and with the *British Journal of Dermatology* [19]. *Clinical & Experimental Dermatology* also publishes summaries of Cochrane reviews.

## Cochrane Skin Group satellites

The Cochrane Collaboration is keen to promote satellite groups around the world who are affiliated to the main editorial bases, to promote evidence-based medicine, Cochrane methods, and to support authors in their countries. We at the UK editorial base are delighted that a French satellite of the CSG was launched in 2012. It will support Cochrane authors in France and in francophone countries, such as Vietnam and Algeria. One of our editors in the USA is currently applying for funding to set up a US satellite of the CSG. In 2010 at the annual CSG meeting, a “comparative effectiveness research” meeting was held in Denver, USA, to promote the concept of evidence-based medicine to American dermatologists. All reviews produced by satellite groups will be submitted to the parent editorial base in Nottingham, UK, and handled like any other Cochrane review.

## Contacting the Cochrane Skin Group editorial base

If you wish to get involved with the CSG, you can do so by doing one or more of the following:

- commenting on published reviews via the feedback facility on *The Cochrane Library*;
- becoming a peer referee for us;
- becoming a review author on a Skin review.

If you are interested, the first thing to do is to contact us at the CSG:

Address: Cochrane Skin Group, The Centre of Evidence-Based Dermatology, Room A103, King's Meadow Campus, University of Nottingham, NG7 2NR

Web: [www.skin.cochrane.org](http://www.skin.cochrane.org)

Email: [csg@nottingham.ac.uk](mailto:csg@nottingham.ac.uk)

Tel: +44 (0) 115 8468627

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## Other useful resources

- The CSG: [www.skin.cochrane.org](http://www.skin.cochrane.org)
- The Cochrane Collaboration: [www.cochrane.org](http://www.cochrane.org)
- The Cochrane Library: [www.thecochranelibrary.com](http://www.thecochranelibrary.com)
- The Cochrane Journal Club: [www.cochranejournalclub.com](http://www.cochranejournalclub.com)
- The Cochrane Handbook for Systematic Reviews of Interventions: [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
- Cochrane training for authors: <http://training.cochrane.org/>
- Cochrane Consumer Network (CCNet): <http://consumers.cochrane.org/>



# PART II

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## The critical appraisal toolbox

Michael Bigby, editor



## CHAPTER 5

# Formulating well-built clinical questions

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### Introduction

Practicing evidence-based medicine (EBM) centers on trying to find answers to clinically relevant questions that arise in caring for individual patients. Asking well-built clinical questions may be the most important step in practicing EBM. To benefit patients and clinicians, the questions need to be directly relevant to the patient's problems and phrased in ways that directs the clinician's search to relevant and precise answers [1].

### Tips for building well-built clinical questions

A well-built clinical question has four elements:

- a patient or problem;
- an intervention;
- a comparison intervention (if necessary); and
- an outcome [1–4].

The first component of a well-built clinical question is an accurate description of the patient and problem. Try to generalize the description balancing precision and brevity [1]. The next two components are accurate descriptions of the relevant intervention or interventions. Interventions can be etiologic factors, diagnostic tests, treatments, prognostic factors, or harmful exposures. Several interventions (e.g., many treatments for psoriasis) might be appropriate for inclusion in the question. When the focus is on treatment, the comparative intervention may be an established treatment, another treatment, or a placebo. The final component of the well-built clinical question is a clinically relevant outcome measure that is important to the patient and treating dermatologist.

One easy way of remembering these key components is the acronym PICO: patient, intervention, comparator, and outcome. Well-built clinical questions about individual patients are not only about treatment; they can be grouped into several categories: etiology, diagnosis, therapy, prevention, prognosis, and harm. For example, a 71-year-old man presents with a painful cluster of vesicles on an erythematous base on his left cheek. You suspect he has herpes zoster, although herpes simplex is in your differential diag-

nosis. Examples of well-built clinical questions about diagnosis, therapy, and prognosis would be:

- 1 In an elderly man presenting with a vesicular eruption, is a viral culture or direct fluorescence antibody test more useful in establishing a diagnosis of herpes zoster?
- 2 In an elderly man with acutely painful herpes zoster, would treatment with antivirals, or antivirals and corticosteroids, lead to more rapid resolution of pain and more rapid return to a normal quality of life?
- 3 If an elderly man who presents with acutely painful herpes zoster is treated with antivirals and corticosteroids or is left untreated, how likely is he to develop post-herpetic neuralgia?

In contrast, examples of poorly structured questions about this same patient would be:

- 4 How do you make a diagnosis of herpes zoster?
- 5 What is the best treatment for herpes zoster?
- 6 What is the prognosis of herpes zoster?

In most clinical situations, several well-built clinical questions are possible using the PICO structure (Table 5.1). It is up to the physician and the patient to determine what are the most important questions.

### The advantages of well-built clinical questions

A major benefit of careful and thoughtful question forming is that it makes the search for evidence and the critical appraisal of the evidence found easier. The well-formed question makes it relatively straightforward to elicit and combine the appropriate terms needed to represent your need for information in the query language of whichever database or search service you choose (e.g., Medline, Embase, or the Cochrane Library). Formulating well-built clinical questions will also train you to clearly define your patient or problem, be specific about the interventions used, and choose carefully described and precise desired outcomes. Questions like those in 4, 5, and 6 above will certainly lead to answers. However,

**Table 5.1** The four elements of a well-built clinical question using the PICO (patient, intervention, comparator, and outcome) structure.

	Patient or problem	Intervention	Comparison intervention (if necessary)	Clinically relevant outcome(s)
Tips for building [1]	Starting with your patient, ask "How would I describe a group of patients similar to mine?" Balance precision with brevity.	Ask "Which main intervention am I considering?"	Ask "What is the main alternative to compare with the intervention?"	Ask "What do I want to accomplish?" or "What could this exposure really affect?"
Example 1: diagnosis	In a patient presenting with a vesicular eruption,	... is a viral culture ...	... or a direct fluorescence antibody (DFA) test ...	... more useful in establishing a diagnosis of herpes zoster?
Example 2 treatment		... would treatment with antivirals ...	... or antivirals and corticosteroids ...	... lead to more rapid resolution of pain and more rapid return to a normal quality of life?
Example 3 prognosis	If an elderly patient with acutely painful herpes zoster ...	... is treated with corticosteroids ...	... or is left untreated, ...	... how likely is s/he to develop post-herpetic neuralgia?

obtaining the answer would require a considerable amount of time searching and validating a vast amount of literature. Structuring the question as in those in 1, 2, and 3 above would lead to more specific answers in considerably less time.

**What factors are important in generating well-built questions in a dermatology consultation?**

A well-built and relevant question can only be generated if there has been an accurate initial evaluation of the patient, which includes a detailed history and examination to establish an accurate diagnosis. The patient's characteristics, such as age, gender, past therapy, general health, or allergies, are important. Understanding which factors are important to the patient (e.g., efficacy of treatment, difficulty of treatment regimen, potential side effects, effect on quality of life, or affordability) is also crucial.

Specifying an outcome that is meaningful to the patient is also important. For example, consider a 28-year-old man with psoriasis who is desperate for a remission of the visible plaques on his body, as he was planning to go for a once-in-a-lifetime holiday to the

coast, where he wanted to expose his skin at the beach. Finding trials that only mention a 50% reduction in the psoriasis area and severity index (PASI) scores as their sole outcome measure would be of little value. What would be of most interest to this man are those trials that specify the percentage of patients achieving complete or nearly complete clearing; for example, a 90% reduction of the PASI after a course of therapy.

Asking a clinically relevant well-built question is not as easy as it might appear. It takes practice and is a learnable skill. Ultimately it saves time, and it is more likely to provide useful answers in caring for individual patients.

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## CHAPTER 6

# Finding the best evidence

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The ability to find the best evidence to answer clinical questions is crucial for practicing evidence-based medicine. Finding evidence requires access to electronic searching, searching skills, and available resources. Methods for finding systematic reviews and evidence about etiology (harm), diagnosis, therapy, prognosis, and clinical prediction guides have been well developed [1,2].

Evidence about therapy is the easiest to find. The best sources for finding the best evidence about treatment include:

- 1 The Cochrane Library;
- 2 searching the Medline and Embase databases;
- 3 primary journals;
- 4 secondary journals;
- 5 evidence-based dermatology and evidence-based medicine books (e.g., clinical evidence);
- 6 the National Guideline Clearinghouse (<http://www.jcaai.org>);
- 7 the National Institute for Health and Clinical Excellence (NICE, [www.nice.org.uk](http://www.nice.org.uk)).

The Cochrane Library contains the Cochrane Database of Systematic Reviews of the Treatment Diseases, the Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane Central Register of Controlled Trials (Central), and the Health Technology Assessment (HTA) database. Volunteers, according to strict guidelines developed by The Cochrane Collaboration, write the systematic reviews in the Cochrane Library. Issue 3 of the 2014 Cochrane Library (accessed 13 March 2014) contained 8367 completed systematic reviews. The number of reviews of dermatological topics is steadily increasing.

Central is a database of over 763 865 controlled clinical trials. It is compiled by searching the Medline and Embase databases, and hand searching many journals. Hand searching journals to identify controlled clinical trials and randomized-controlled clinical trials was undertaken because members of The Cochrane Collaboration noticed that many trials were incorrectly classified in the Medline database. As an example, Dr Finola Delamere of the Cochrane Skin Group, hand searched the *Archives of Dermatology* from 1990 through 1998 and identified 99 controlled clinical trials. Nineteen of the trials were not classified as controlled clinical trials in Medline and 11 trials that were not controlled clinical trials were misclassified as control clinical trials in Medline [3].

DARE is a database of abstracts of systematic reviews published in the medical literature. It contained abstracts and bibliographic details on 28 388 published systematic reviews. DARE is the only database to contain abstracts of systematic reviews that have been quality assessed. Each abstract includes a summary of the review together with a critical commentary about the overall quality.

The HTA database consists of completed and ongoing health technology assessments (studies of the medical, social, ethical, and economic implications of health-care interventions) from around the world. It contained 13 138 assessments in issue 2 of the 2013 Cochrane Library. The aim of the database is to improve the quality and cost effectiveness of health care.

The Cochrane Library is the best source for evidence about treatment. It can be easily searched using simple Boolean combinations of search terms and by more sophisticated search strategies. The Cochrane Database of Systematic Reviews, DARE, Central, and HTA can be searched simultaneously. The Cochrane Library is available on a personal or institutional subscription basis on DVD, and on the World Wide Web from Wiley InterScience (<http://www.thecochranelibrary.com/view/0/HowtoOrder.html>). The Cochrane Library is updated quarterly. The Cochrane Library is offered free of charge in many countries by national provision and by many medical schools in the USA. It should be available at your medical library.

The second best method for finding evidence about treatment and the best source for finding most other types of best evidence in dermatology is by searching the Medline database by computer [2,4]. Medline is the National Library of Medicine's (NLM's) bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health-care system, and the pre-clinical sciences. The Medline file contains bibliographic citations and author abstracts from approximately 5600 current biomedical journals published in the USA and 80 other countries. The file contains approximately 19 million records dating back to 1946 [5].

Medline searches have inherent limitations that make their reliability less than ideal [2]. For example, Spuls *et al.* conducted a systematic review of systemic treatments of psoriasis [6]. Treatments analyzed included UVB, PUVA, methotrexate, cyclosporin A, and retinoids. The authors used an exhaustive strategy to find relevant

references, including Medline searches, contacting pharmaceutical companies, polling leading authorities, reviewing abstract books of symposia and congresses, and reviewing textbooks, reviews, editorials, guideline articles, and the reference lists of all papers identified. Of 665 studies found, 356 (54%) were identified by Medline search (range 30–70% for different treatment modalities). The 17 of 23 authorities who responded provided no references beyond those identified by Medline searching.

The key to Medline searching is to find relevant articles and to exclude irrelevant citations. Several useful techniques can greatly aid your ability to accomplish this goal. Searches generally are done on the basis of Boolean combinations of search terms. For example, a search for best evidence about drug treatment of onychomycosis might read [onychomycosis and (terbinafine or itraconazole or fluconazole) not case reports].\* This search would identify articles on onychomycosis using any of the listed drugs and excluding case reports [1,2].

It is important to understand the difference between text word and Medical Subject Headings (MeSH) searching and to be able to do both. Many of the programs used to search the Medline database automatically do text word and MeSH searches. MeSH terms includes all of the terms in the Medical Subject Headings, a controlled vocabulary of keywords used to index Medline. Each Medline citation is given a group of MeSH terms that relate to the subject of the paper from which it is drawn. Frequently, MeSH terms will have an additional subheading, which further defines how the MeSH term relates to the article with which it is associated. This subheading is appended to the MeSH term; for example, “onychomycosis diagnosis.”

Indexing articles is not an exact science. The MeSH headings assigned by the NLM may not coincide with the intent of the author or the majority of searchers for several reasons. Authors may not clearly express their intent, indexers are usually not experts in the field of the article they are indexing, and the mistakes associated with doing repetitive tasks occur [2]. Relevant articles may be missed when they are not assigned the appropriate MeSH heading. Irrelevant articles may be included in a MeSH search if they are assigned to the wrong MeSH heading. For example, The Cochrane Collaboration identified major problems in the Medline indexing of randomized controlled trials [2].

Text word searches allow one to search articles for words within the title and abstract that are important to and coincide with the intent of the author. However, text word searches are subject to several problems. Authors may not describe their methods or objectives well or may make errors in spelling, omission, or commission [2]. The problem of misspelling can be illustrated by doing a text word search for “pruritis” (pruritus spelled incorrectly). This search will yield 114 references in which the word has been misspelled. Many of these references may not be detected in a search for pruritus (spelled correctly) [2].

Boolean topic searches will often contain too many references or too few. They may contain many irrelevant citations and miss many relevant citations. Several techniques will help make searches more sensitive (i.e., pick up relevant citations) and more specific (i.e., exclude irrelevant citations) [2]. To increase the sensitivity of searches, searching both text word and MeSH headings, exploding MeSH headings and using truncation may be helpful. MeSH term searches can be “exploded” to include all terms that are logical

subsets of the term entered [2]. For example, exploding the MeSH term “onychomycosis” will retrieve all of the articles that use that MeSH term, whether they have subheadings or not. Many of the programs used to search the Medline database automatically explode searches of MeSH terms or MeSH Major Topics.

Truncation refers to searching using the root of a word to allow variants of the word to be detected. For example, a search of onychomycosis and controlled clinical trial will detect fewer studies than a search for onychomycosis and control\* (where control\* contains a wild card that will allow detection of all words that begin with the root “control”). Truncation can be performed on text word and MeSH heading searches.

To increase the specificity of searches, selecting specific subheadings of MeSH terms and limiting the search may be helpful. MeSH terms can be limited to specific subheadings to help narrow search results to relevant articles. For example, onychomycosis has subheadings that restrict retrieved articles to ones dealing with diagnosis or drug treatment [2]. Searches can be limited in many ways, including publication type, language, human subjects, and date of publication. Restricting the publication type to randomized controlled trial or case-control study is useful to limit retrieved articles to those of highest quality.

Performing a sensitive or specific search from scratch is often a time-consuming task. Arriving at an efficient search strategy to suit one’s particular needs is sometimes a work of art. Once accomplished, it is important to be able to edit, save, and retrieve the search strategy. The saved strategy can then be used in future searches of different subjects without having to rethink or retype the whole search procedure. The methods for performing these techniques (text word and MeSH searching, exploding, truncation, using subheadings, limiting, and saving) vary by platform used. Mastering them will greatly improve searching efficiency.

Specific search strategies, “filters,” have been developed to help find relevant references and exclude irrelevant references for best evidence about etiology, diagnosis, therapy, prognosis, and clinical prediction guides, and for finding systematic reviews ([http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.Clinical\\_Queries\\_Filters](http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.Clinical_Queries_Filters)) [7,8]. Each type of search can be made narrow (specific) or broad (sensitive). These filters have been incorporated into the PubMed Clinical Queries search engine of the NLM and are available at <http://www.ncbi.nlm.nih.gov/pubmed/clinical> [5]. *PubMed Clinical Queries is the preferred method for searching the Medline database for best, clinically relevant evidence.* It can be freely used by anyone with Internet access.

Clinicians are increasingly using general search engines such as Google, Bing, or Google Scholar to search the Internet for medical information [9]. These search engines are not specifically designed to find the types of evidence needed for clinical decision making. They are much less sensitive and specific in finding clinically useful evidence when compared with PubMed searches with Clinical Queries filters [10].

Embase is Excerpta Medica’s database covering drugs, pharmacology, and biomedical specialties [11]. Embase has better coverage of European and non-English language sources and may be more up to date [11]. The overlap in journals covered by Medline and Embase is about 34% (range 10–75% depending on the subject) [2]. Embase contains over 27 million records from 1947 to the present. Embase is available online (<http://www.embase.com/>).

\* The convention used throughout for search entries is that Boolean operations within parentheses are done first.

Personal and institutional subscriptions are available. Embase.com performs simultaneous searches of Embase and Medline databases and eliminates duplicate records. The filters that are incorporated into the PubMed Clinical Queries search engine can be used to perform clinically relevant searches of Embase with some modification [2,7,8].

Structured abstracts of articles are published in secondary journals (e.g. the Evidence-based Dermatology section of *JAMA Dermatology* and the *British Journal of Dermatology*). The articles are strictly selected on the basis of methodological quality and are accompanied by commentary putting the information in clinical perspective.

Full text versions of many primary journals are now available on the Internet. Access is made available in many hospitals and medical school libraries. Available commercial vendors include Science Direct (<http://www.sciencedirect.com/>), Highwire (<http://highwire.stanford.edu/>), and EBSCO Publishing (<http://www.ebscohost.com/academic/medline-with-full-text>), among others.

The National Guideline Clearinghouse maintains a database of guidelines for the treatment of disease written by panels of experts following strict guidelines of evidence. The database is accessible through the Internet (<http://guideline.gov/>). There are currently more than 100 dermatological topics; however, many have not been recently updated.

NICE (<http://www.nice.org.uk/>) produces guidance on public health, health technologies, and clinical practice based on the best available evidence. Its coverage of dermatological topics is limited,

but it includes guidance for treating atopic eczema, a final appraisal determination on the use of calcineurin inhibitor for atopic dermatitis, the use of biologics for psoriasis, and a full set of guidelines for skin cancer, including melanoma.

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## CHAPTER 7

# The hierarchy of evidence

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Once appropriate questions have been formulated, what is the best evidence to answer these questions? Potential evidence includes personal experience, colleagues or experts, textbooks, and articles published in journals. An important principle of evidence-based medicine (EBM) is the concept of a *hierarchy of evidence* (i.e., that there is a hierarchy in the quality [strength] of evidence) (Figure 7.1) [1,2]. Systematic reviews are scientific summaries of the quality, direction, magnitude, and precision of the evidence. The ordering of the hierarchy of evidence has been widely discussed, actively debated, changed, and sometimes hotly contested [3–7].

Well-conducted systematic reviews of well-performed clinical studies (especially if the studies have results of similar magnitude and direction, and if they are comparable) are most likely to have results that are true and useful. A systematic review is an overview that answers a specific clinical question, contains a thorough, unbiased search of the relevant literature, explicit criteria for assessing studies, and a structured presentation of the results. A systematic review that uses quantitative methods to summarize results is a meta-analysis [3,8].

Meta-analysis allows one to recognize important treatment effects by combining the results of small trials that individually lack the power to demonstrate differences among treatments. For example, the benefits of intravenous streptokinase in acute myocardial infarction were recognized by the results of a cumulative meta-analysis of smaller trials at least a decade before experts recommended it and before large clinical trials showed it to be efficacious [3,4].

Meta-analysis has been criticized for the discrepancies between the results of meta-analysis and the results of large clinical trials [3,5–7]. For example, the results of a meta-analysis of 14 small studies of calcium to treat preeclampsia showed that treatment was effective, whereas a large trial failed to show a treatment effect [3]. The frequency of discrepancies ranges from 10% to 23% [3]. Discrepancies can often be explained by differences in treatment protocols, heterogeneity of study populations, or changes that occur with time [3].

Not all systematic reviews and meta-analyses are equal. Systematic reviews performed in The Cochrane Collaboration are rated among the best, but even then up to a third may contain significant prob-

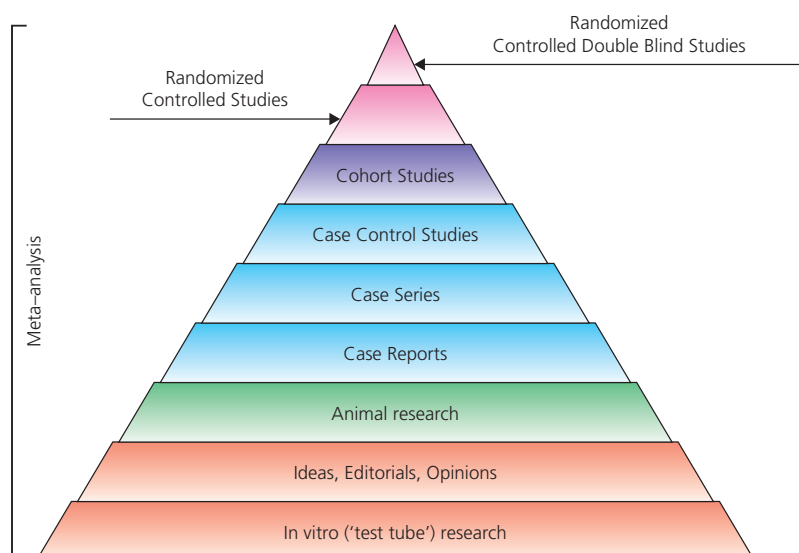
lems [9,10]. Methods exist for assessing the quality of systematic reviews (see Chapter 8) [2,11].

The type of clinical study that constitutes best evidence is determined by what type of question is being asked (Table 7.1) [12]. Questions about diagnosis are best addressed by cohort studies, which include comparisons with a reference standard evaluated in an appropriate spectrum of patients in whom the test is likely to be used [2,11,13,14]. Questions about therapy and prevention are best addressed by randomized controlled trials (RCTs) [2,11,15,16]. Cohort studies or case-control studies best address questions about prognosis, harm, and disease etiology [2,11,17,18]. Methods exist for assessing the quality of each type of evidence (see Chapters 9–14) [2,11].

The randomized controlled clinical trial became the gold standard for determining treatment efficacy in 1948, with the publication of the trial that demonstrated that streptomycin was effective in the treatment of pulmonary tuberculosis [19]. Over 763 865 RCTs are recorded in the Cochrane Controlled Trials Registry, and thousands more exist in an unpublished form [20]. Large, inclusive trials that have concealed randomization, are fully blinded, have clinically relevant outcomes, intention-to-treat analysis, and equal treatment of randomized groups are likely to provide the best possible evidence about effectiveness [21–23]. Studies have demonstrated that failure to use randomization or adequate concealment of allocation resulted in larger estimates of treatment effects, often because of a poorer prognosis in nonrandomly selected control groups in comparison with randomly selected control groups [23].

Expert opinion can be valuable, particularly for rare conditions in which the expert has the most experience or when other forms of evidence are not available. However, several studies have found that expert opinion often lags significantly behind conclusive evidence [1]. Experts should be aware of the quality of existing evidence.

Whereas personal experience is an invaluable part of becoming a competent physician, the pitfalls of relying too heavily on personal experience are widely documented [1,24,25]. Nisbett and Ross extensively reviewed people's ability to draw inferences from personal experience and documented several pitfalls [26]. They include:



**Figure 7.1** The evidence pyramid. Reproduced from SUNY Downstate Medical Center, Medical Research Library of Brooklyn Guide to Research Methods. The Evidence Pyramid. SUNY Health Sciences, Evidence Based Medicine Course <http://library.downstate.edu/EBM2/2100.htm>.

**Table 7.1** Strength of recommendation taxonomy (SORT) based on levels of evidence.

Strength of recommendation	Level of evidence needed	Definitions		
		Treatment/prevention	Diagnosis	Prognosis
A Recommendation based on consistent and good-quality patient-oriented evidence. <sup>a</sup>	1. Consistent and good patient-oriented evidence.	Systematic review (SR)/ meta-analysis of RCTs with consistent findings. High-quality individual RCT. <sup>b</sup> All-or-none study. <sup>c</sup>	Validated clinical decision rule. SR/meta-analysis of high-quality studies. High-quality diagnostic cohort study. <sup>d</sup>	SR/meta-analysis of good-quality cohort studies. Prospective cohort study with good follow-up.
B Recommendation based on inconsistent or limited-quality patient-oriented evidence. <sup>a</sup>	2. Inconsistent or limited-quality patient-oriented evidence.	SR/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings. Lower-quality clinical trial. <sup>b</sup> Cohort study. Case-control study.	Unvalidated clinical decision rule. SR/meta-analysis of lower-quality studies or studies with inconsistent findings. Lower-quality diagnostic cohort study or diagnostic case-control study. <sup>c</sup>	SR/meta-analysis of lower-quality cohort studies or with inconsistent results. Retrospective cohort study or prospective cohort study with poor follow-up. Case-control study. Case series.
C Recommendation based on other evidence.	3. Other evidence.	Consensus, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening.		

Reproduced from Ebell *et al.* [12], with permission from American Academy of Family Physicians.

<sup>a</sup>Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).

<sup>b</sup>High-quality RCT: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%).

<sup>c</sup>In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appendicitis, which precludes study in a controlled trial.

<sup>d</sup>High-quality diagnostic cohort study: cohort design, adequate size, adequate spectrum of patients, blinding, and a consistent, well-defined reference standard.

\*By homogeneity, we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.

<sup>†</sup>Met when *all* patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but *none* now die on it.

- overemphasis of vivid anecdotal occurrences and underemphasis of significant statistically strong evidence;
- bias in recognizing and accepting evidence that supports one's own beliefs, and parallel failure to recognize or accept evidence that contradicts one's own beliefs;
- persistence of beliefs in spite of overwhelming evidence presented against them.

Textbooks appear to be a valuable source of evidence, but they have serious shortcomings. First, by virtue of the way in which they

are written, produced, and distributed, most are about 2 years out of date at the time of publication. Most textbook chapters are narrative reviews that do not consider the quality of the evidence reported [1,2]. They tend to reflect the biases and shortcomings of the experts who write them.

More detailed studies of the relationship of study type and the direction and magnitude of purported benefit are needed in dermatology to guide dermatologists on the relative merits of different study designs. In the meantime, the hierarchy of evidence should

not be conceptualized as a linear phenomenon (i.e., as a scale going from “good” to “bad”). The quality and relevance of evidence should be considered. Thus, a well-conducted large cohort study may be more reliable than a small RCT that has violated most aspects of good RCT design and reporting. Similarly, a small RCT of moderate quality dealing with the exact problem about which the patient is complaining (e.g., palmoplantar psoriasis) is likely to be more useful than a large RCT dealing with a different or broader problem (e.g., psoriasis).

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# Appraising systematic reviews and meta-analyses

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## Introduction

A systematic review is an overview that answers a specific clinical question, contains a thorough, unbiased search of the relevant literature, explicit criteria for assessing studies, and structured presentation of the results. Put simply, a systematic review is a review that is done systematically. A systematic review that incorporates quantitative pooling of several similar studies to produce an overall summary of treatment effects is a meta-analysis [1,2]. Meta-analysis provides an objective and quantitative summary of evidence that is amenable to statistical analysis [1]. Meta-analysis allows recognition of important treatment effects by combining the results of small trials that individually might have lacked the power to consistently demonstrate differences among treatments. In conducting a meta-analysis, authors should recognize the importance of having clear objectives, explicit criteria for study selection, an assessment of the quality of included studies, and criteria for which studies can be combined. Meta-analysis is not appropriate if the included studies are very different. Meta-analyses that are not conducted within the context of a systematic review should be viewed with great caution [3].

In summary, a systematic review can be viewed as a scientific and systematic examination of the available evidence. A good systematic review will have explicitly stated objectives (the focused clinical question), materials (the relevant medical literature), and methods (the way in which studies are assessed and summarized). The steps taken during a systematic review are shown in Table 8.1. Just like good randomized controlled trials, protocols describing the plans of a systematic review should be published in the public domain before the review is undertaken, in order to avoid *post hoc* data dredging and biased reporting of results. Such is the practice of The Cochrane Collaboration, where protocols and completed reviews can be compared ([www.thecochranelibrary.com](http://www.thecochranelibrary.com)), along with forced headings in the completed review for the reader to see where the final review has departed from the published protocol along with reasons. Protocols for systematic reviews that are not published in the *Cochrane Library* should be registered with PROSPERO – an international prospective register for systematic reviews based at the Centre of Reviews and Dissemination in York, UK <http://www.crd.york.ac.uk/PROSPERO/>.

Not all systematic reviews and meta-analyses are equal. A systematic review should be conducted in a manner that will include all of the relevant trials (including unpublished trials), minimize the introduction of bias, and synthesize the results to be as truthful as possible and as useful to clinicians as possible. The criteria for critically appraising systematic reviews and meta-analyses are shown in Table 8.2. In general, these criteria are similar to the criteria used to appraise the individual studies that make up the systematic review. Detailed explanations of each criterion are available [1,4]. Other tools, such as AMSTAR (“assessment of multiple systematic reviews”), have been developed to assess the methodological quality of systematic reviews, building upon previous tools, empirical evidence, and expert consensus [5].

The quality of reporting of systematic reviews is highly variable. One cross-sectional study of 300 systematic reviews published in Medline by Moher *et al.* showed that over 90% were reported in specialty journals [6]. Funding sources were not reported in 40% of reviews. Only two-thirds reported the range of years that the literature was searched for trials. Around a third of reviews failed to provide a quality assessment of the included studies, and only half of the reviews included the term “systematic review” or “meta-analysis” in the title. Similar results have been found for dermatological systematic reviews of common skin disorders [54].

Guidelines for better reporting of systematic reviews were established in 1999 by the Quality of Reporting of Meta-Analyses initiative and revised in 2009 [7,8] – preferred reporting items for systematic reviews and meta-analyses (PRISMA). Many journals now insist on reporting systematic reviews in accordance with the PRISMA checklist [8].

## Asking a clear question

Like the well-built clinical question for individual studies, a focused clinical question for a systematic review should contain four elements:

- a patient, group of patients, or problem;
- an intervention;
- comparison interventions;
- specific outcomes [9].

The patient populations should be similar to the majority of patients seen in the population to which one wishes to apply the results of the systematic review. The interventions studied should ideally be those commonly available in practice. Outcomes reported should be those that are most relevant to physicians and patients. Main outcomes should be previously specified in a published protocol, in order to avoid problems with *post hoc* data dredging.

### Sources of evidence within a systematic review

The majority of systematic reviews in dermatology involve therapy, although systematic reviews of diagnostic tests [10], etiology [11], and even mechanisms [12] are emerging. Randomized, controlled clinical trials should be used for systematic reviews of therapy if they are available, because they are generally less susceptible to selection and information bias in comparison with other study designs. The quality of included trials is assessed using the criteria that are used to evaluate individual randomized, controlled clinical trials. The quality criteria commonly used include concealed, random allocation; groups similar in terms of known prognostic factors; equal treatment of groups; blinding of patients, researcher, and analyzers of the data to treatment allocation; and accounting for all patients entered into the trial when analyzing the results (intention-to-treat design). In Cochrane reviews, graphical “risk of bias” displays are provided of how these key elements vary according to included studies [13].

**Table 8.1** The steps involved in undertaking a systematic review.

1 Asking a clear, focused question
2 Formulating the methods by which the evidence will be found, appraised, analyzed, and reported
3 An explicit and thorough search of the literature
4 Data extraction
5 Critical appraisal of the quality of the primary studies and of their results
6 Reporting the results with quantitative pooling of the data, if appropriate
7 Interpretation of the data, including implications for clinical practice and further research

Randomized controlled trials are rarely a reliable source for identifying adverse reactions, unless they are very common. Evidence sources such as case-control studies, case reports, and postmarketing surveillance studies should therefore be examined [14]. Systematic reviews of treatment efficacy should always include a thorough assessment of common and serious adverse events as well as efficacy, in order to come to an informed and balanced decision about the utility of a treatment. A thorough assessment of adverse events should include data from randomized controlled trials, case-control and postmarketing surveillance studies, and some of the other sources shown in Table 8.3.

### The hazards of “quick” searches

A sound systematic review can be performed only if most or all of the available data are examined. An explicit and thorough search of the literature should be performed. It should ideally include searching several electronic bibliographic databases, no language restrictions, scrutiny of citation lists in retrieved articles,

**Table 8.2** Critical appraisal of a systematic review.

#### Are the results of this systematic review valid?

- Did the review address a focused clinical question?\*
- Were the criteria used to select articles for inclusion appropriate?\*
- Is it unlikely that important, relevant studies were missed?†
- Was the validity of the included studies appraised?†
- Were assessments of studies reproducible?†
- Were the results similar from study to study?†

#### Are the valid results of this systematic review important?

- What are the overall results of the review in terms of magnitude of benefit or harm?
- How precise were the results?

#### Can you apply this valid, important evidence in caring for your patient?

- Can the results be applied to my patient's care?
- Were all clinically important outcomes considered?
- Are the benefits worth the harms and costs?

Reproduced from Sackett *et al.* [4], with permission from Elsevier.

\* Primary guides.

† Secondary guides.

**Table 8.3** Other sources for data on adverse reactions to drugs.

Resource	Source	Comments
<i>Martindale: The Complete Drug Reference</i>	<a href="http://www.pharmpress.com/">http://www.pharmpress.com/</a>	37th edition. 2011
<i>Meyler's Side Effects of Drugs</i>	<a href="http://www.elsevier.com">http://www.elsevier.com</a>	15th edition. 2006
<i>Side Effects of Drugs</i> annuals	<a href="http://www.elsevier.com">http://www.elsevier.com</a>	Data 1–2 years old
<i>Reactions Weekly</i>	ADIS Press: <a href="http://www.ovid.com">http://www.ovid.com</a>	Requires registration and fee
<i>Drug Safety Update</i>	<a href="http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/index.htm">http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/index.htm</a>	Drug safety bulletin of the Medicines and Healthcare Products Regulatory Agency and the Commission on Human Medicines. Issues freely searchable
<i>Medicines Safety Update</i>	<a href="http://www.tga.gov.au/hp/aadrb.htm">http://www.tga.gov.au/hp/aadrb.htm</a>	Back issues and free e-mail subscription available
European Public Assessment Reports	<a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&amp;mid=WCOb01ac058001d125">http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&amp;mid=WCOb01ac058001d125</a>	Free, searchable database of reports
MedWatch	<a href="http://www.fda.gov/Safety/MedWatch/default.htm">http://www.fda.gov/Safety/MedWatch/default.htm</a>	Free searchable database of spontaneous reports of adverse reactions to drugs, maintained by the US Food and Drug Administration



hand-searching for conference reports, prospective trial registers, contacting key researchers, authors, and drug companies.

Simply performing a quick Medline search using “clinical trial” as the publication type is rarely adequate, because complex and sensitive search strategies are needed in order to identify all potential trials, and because some clinical trials will be missed if they are published in a journal not listed by Medline [15]. Potential sources for finding studies about treatment include: the Cochrane Central Register of Controlled Trials (CENTRAL), which is part of the *Cochrane Library*, Medline, Embase, Literatura Latino Americana em Ciências da Saúde (LILACS), bibliographies of studies, review articles and textbooks, symposia proceedings, ongoing trial registries (such as those included in the WHO International Clinical Trials Registry Platform), pharmaceutical companies, and contacting experts in the field.

CENTRAL is a database of over 763 865 controlled clinical trials (March 2014) and is the largest and most complete database of clinical trials worldwide. CENTRAL has been compiled through several complex searches of the Medline and Embase databases, and by hand-searching many journals – a process that is quality controlled and monitored by The Cochrane Collaboration. Hand-searching journals to identify controlled clinical trials and randomized, controlled clinical trials was undertaken because members of The Cochrane Collaboration noticed that many trials were incorrectly classified in the Medline database. As an example, Adetugbo *et al.* hand-searched the journal *Clinical and Experimental Dermatology* for randomized controlled trials from its inception in 1976 through 1997 and identified 73 controlled clinical trials, yet only 31 of these could be identified from a Medline search using “clinical trial” as the publication type [16].

Medline is the National Library of Medicine bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health-care system, and the preclinical sciences. The Medline file contains bibliographic citations and author abstracts from approximately 5600 current biomedical journals published in the USA and 80 other countries. The file contains approximately 20 million records, dating back to the mid 1940s (<http://www.nlm.nih.gov/pubs/factsheets/medline.html>).

Embase is Excerpta Medica’s database covering drugs, pharmacology, and biomedical specialties [1]. Embase has better coverage of European and non-English-language sources and may be more up to date [1]. The overlap in journals covered by Medline and Embase is about 34% (range 10–75%, depending on the subject) [13,17]. Embase contains over 25 million records from 7000 journals from 1947 to the present. Embase is available online (<http://www.embase.com>). Personal and institutional subscriptions are available. Embase.com performs simultaneous searches of the Embase and Medline databases and eliminates duplicate records.

LILACS is a database covering more than 600 medical journals from the Latin America and Caribbean region. LILACS can be searched free of charge in Spanish, Portuguese, and English (<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F>). Many of the journals covered are not included in other databases.

## Publication and selective reporting outcome bias

Publication bias (i.e., the tendency that studies that show positive effects are more likely to be published and are easier to find) is an important concern for systematic reviews, and a useful review of

this subject can be found elsewhere [18]. It results from allowing factors other than the quality of the study to influence its acceptability for publication. Several studies have shown that factors such as the sample size, financial conflicts of interest, the direction and statistical significance of findings, or the investigators’ perceptions of whether the findings are “interesting” are related to the likelihood of publication [19,20].

Language bias may also be a problem – that is, the tendency for studies that are “positive” to be published in an English-language journal and also more quickly than inconclusive or negative studies [21]. A thorough systematic review should therefore include a search for high-quality unpublished trials and should not restrict itself to journals published in English.

Studies with small samples are less likely to be published, especially if they have negative (or more often inconclusive) results [19,20]. By emphasizing only those studies that are positive, this type of publication bias jeopardizes one of the main goals of meta-analysis (i.e., an increase in power when pooling the results of small studies). The creation of study registers (e.g., those included in the WHO International Clinical Trials Registry Platform, <http://www.who.int/ictpr/en/>) and advance publication of research designs have been proposed as ways to prevent publication bias [22,23].

Methods for exploring the publication bias include the use of a simple graphic test (funnel plot), by calculating the fail-safe *N*, Begg’s rank correlation method, Egger regression method, and others. [24,25] These techniques are of limited value when less than 10 randomized controlled trials are included. Rigorous testing for publication bias is often not possible in systematic reviews of skin diseases, owing to the limited number and sizes of trials.

For many diseases, the studies published are dominated by drug-company-sponsored trials of new, expensive treatments. Such studies are almost always “positive” [26,27]. Such a bias in publication can result in data-driven systematic reviews that draw more attention to those medicines. In contrast, question-driven systematic reviews answer the clinical questions of most concern to practitioners. In many cases, studies that are of most relevance to doctors and patients have not been done in the field of dermatology, owing to inadequate sources of independent funding. Systematic reviews that have been sponsored directly or indirectly by industry are also prone to bias through overinclusion of unpublished “positive” studies that are kept “on file” by that company [28]. Until it becomes mandatory to register all clinical trials conducted on human beings in a central registry and to make all of the results available in the public domain, distortions may occur due to selective withholding or release of data. Thankfully, some dermatology journals now require all their published trials to have been registered beforehand.

Selective reporting outcome bias – the tendency to highlight only those outcomes out of many that look positive after the analysis has been done – is another serious concern, not only in randomized controlled trials [29], but also in systematic reviews. For example, in the absence of a pre-published systematic review protocol as is required in Cochrane reviews, it is impossible to say whether the outcomes of a published review reflect the important ones that were selected before the review was done, or whether they simply reflect a data-driven process simply because those were the outcomes that looked best [30].

Generally, reviews that have been conducted by volunteers in The Cochrane Collaboration are of better quality than non-Cochrane reviews [31,32]. However, potentially serious errors have been noted in up to a third of such reviews [33].

## Data abstraction

In general, the studies included in systematic reviews are reviewed by at least two reviewers for eligibility, according to prespecified inclusion and exclusion criteria. Data such as the numbers of people entered into studies, numbers lost to follow-up, effect sizes, and quality criteria are recorded on predesigned data abstraction forms by at least two reviewers. Differences among reviewers are usually settled by consensus or by a third arbitrator. A systematic review in which there are large areas of disagreement among reviewers should lead the reader to question the validity of the review.

## Pooling results

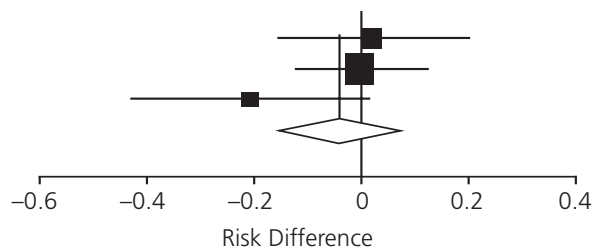
Results in the individual clinical trials that make up a systematic review may be similar in magnitude and direction (e.g., they may all indicate that treatment A is superior to treatment B by a similar magnitude). Assuming that publication bias can be excluded, systematic reviews with studies that have results that are similar in magnitude and direction provide results that are most likely to be true and useful. It may be impossible to draw firm conclusions from systematic reviews in which studies have results of widely different magnitude and direction.

The magnitude of the difference between the treatment groups in achieving meaningful outcomes is the most useful summary result of a systematic review. The most easily understood measures of the magnitude of the treatment effect are the difference in response rate and its reciprocal, the number needed to treat (NNT) [1,4]. The NNT represents the number of patients one would need to treat in order to achieve one additional cure. Whereas the interpretation of NNT might be straightforward within one trial, interpretation of NNT requires some caution within a systematic review, as this statistic is highly sensitive to baseline event rates. For example, if a treatment A is 30% more effective than treatment B for clearing psoriasis, and 50% of people on treatment B are cleared with therapy, then 65% will clear with treatment A. These results correspond to a rate difference of 15% (65% – 50%) and an NNT of 7 (1/0.15). This difference sounds quite worthwhile clinically. But if the baseline clearance rate for treatment B in another trial or setting is only 30%, the rate difference will be only 9% and the NNT now becomes 11, and if the baseline clearance rate is 10%, then the NNT for treatment A will be 33, which is perhaps less worthwhile. In other words, it rarely makes sense to provide one NNT summary measure within a systematic review, because “control” or baseline event rates usually differ considerably between studies, due to differences in study populations, interventions, and trial conditions [34]. Instead, a range of NNTs for a range of plausible control event rates that occur in different clinical settings should be given, along with their 95% confidence intervals, as can be found for “summary of findings” tables used in Cochrane systematic reviews produced since 2011 [35]. Further examples of NNTs in dermatology are to be found elsewhere [36].

The precision of the estimate of the differences among treatments should be estimated. The confidence interval provides a useful measure of the precision of the treatment effect [1,4,37,38]. The calculation and interpretation of confidence intervals have been extensively described [38]. In simple terms, the reported result (known as the “point estimate”) provides the best estimate of the treatment effect. The population or “true” response to treatment will most likely lie near the middle of the confidence interval and will rarely be found at or near the ends of the interval. The population or true response to treatment has only a 1 in 20 chance of being outside of the 95% confidence interval.

The point estimates and confidence intervals of the individual trials and the synthesis of all trials are typically displayed graphically in a forest plot (Figure 8.1) [39]. Results are often expressed as the odds ratio of the treatment effect (i.e., the odds of achieving a good outcome in the treated group divided by the odds of achieving a good result in the control group) but can be expressed as risk differences (i.e., difference in response rate) or relative risk (probability of achieving a good outcome in the treated group divided by the probability in the control group). Because odds ratios tend to overestimate the true risk if the outcomes are common, as in many dermatology settings [40], relative risk is most often used in Cochrane Skin Group reviews. A relative risk (or odds ratio) of 1 (null) indicates no difference between treatment and control and is usually represented by a vertical line passing through 1 on the x-axis. A relative risk of greater than or less than 1 implies that the treatment is superior or inferior to the control respectively. The point estimate of individual trials is indicated by a square whose size is proportional to the size of the trial (i.e., number of patients analyzed). The precision of the trial is represented by the 95% confidence interval that appears in forest plots as the brackets surrounding point estimate. If the 95% confidence interval (brackets) does not cross null (relative risk of 1), then the individual trial is statistically significant at the  $P = 0.05$  level [39]. The summary value for all trials is shown graphically as a parallelogram whose size is proportional to the total number of patients analyzed from all trials. The lateral tips of the parallelogram represent the 95% confidence interval, and if they do not cross null (relative risk of 1) then the summary value of the meta-analysis is statistically significant at the  $P = 0.05$  level. Relative risks and odds ratios can be converted to risk differences and NNTs if the event rate in the control group is known (<http://www.cebm.net/index.aspx?o=1044>).

Certain conditions must be met when meta-analysis is performed to synthesize results from different trials. The trials should have conceptual homogeneity. They must involve similar patient populations, have used similar treatments, and have measured results in a similar fashion at a similar point in time. There are two main statistical methods by which results are combined: using random-effects models and fixed-effects models. Random-effects models assume that the different studies’ results may come from different populations with varying responses to treatment. Fixed-effects models assume that each trial represents a random sample of a single population with a single response to treatment. In general, random-effects models are more conservative (i.e., random-effects models are less likely to show statistically significant results than fixed-effects models). When the combined studies have statistical homogeneity (i.e., when the studies are reasonably similar



**Figure 8.1** Typical forest plot showing the results of a meta-analysis of trials of tacrolimus 0.1% ointment versus vehicle in the management of moderate to severe atopic dermatitis. The X-axis represents the rate ratio of the investigator global assessment of response. Reproduced from Ashcroft *et al.* [53], with permission from the BMJ.

in direction, magnitude, and variability), random-effects and fixed-effects models give similar results.

The key principle when considering combining results from several studies together is that conceptual homogeneity precedes statistical homogeneity. In other words, results of several different studies should not be combined if it does not make sense to combine them – for example, if the patient groups or interventions studied are not sufficiently similar to each other. Although what constitutes “sufficiently similar” is a matter of judgment, the important thing is to be explicit about one’s decision to combine or not combine different studies. Tests for statistical heterogeneity are typically of low power, so that statistical homogeneity does not mean clinical homogeneity. Statistical heterogeneity is typically measured in Cochrane reviews using the  $I^2$  statistic [41], with values of greater than 50% representing substantial heterogeneity. When evidence of heterogeneity is found, reasons for heterogeneity between studies – such as different disease subgroups, intervention dosage, or study quality – should be sought [42].

Sometimes, the robustness of an overall meta-analysis is tested further by means of a sensitivity analysis. In a sensitivity analysis, the data are reanalyzed, excluding those studies that are of low quality or because of certain patient factors such as disease subtype, to see whether their exclusion makes a substantial difference in the direction or magnitude of the main original results. In some systematic reviews in which a large number of trials have been performed, it is possible to evaluate whether certain subgroups (e.g., children vs adults) are more likely to benefit than others. Subgroup analysis is rarely possible in dermatology, because few trials are available. Subgroup analyses should always be prespecified in a systematic review protocol in order to avoid spurious post hoc claims. In very large systematic reviews, it is sometimes possible to determine which factors predict the magnitude of treatment success by a form of analysis known as meta-regression [43].

## Interpretation of the data

The conclusions in the discussion section of a systematic review should closely reflect the data that have been presented within that review. The authors should make it clear which of the treatment recommendations are based on the review data and which reflect their own judgments. Cochrane reviews now also include a “summary of findings” table, in addition to the review abstract and lay summary, which summarizes the key information on the quality of evidence, the magnitude and direction of effect of the interventions examined, and the sum of available data on all important outcomes for a given comparison. The quality of evidence in a summary of findings table is usually graded as high, moderate, low, or very low on applying the five criteria (limitations in the design suggesting high likelihood of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias) as recommended by the Grading of Recommendations Assessment, Development and Evaluation working group [44].

In addition to making clinical recommendations of therapies when evidence exists, many reviews in dermatology find little evidence to address the questions posed. A lack of conclusive evidence does not mean that the review is a waste of time, especially if the question addressed appears to be an important one [45]. For example, the systematic review of antistreptococcal therapy for guttate psoriasis provided the authors with an opportunity to call for primary research in this area, and to make recommendations

on study design and outcomes that might help future researchers [46]. Some reviewers have gone into more depth in using systematic reviews of many inconclusive quality studies to suggest key aspects of study design relating to patients, intervention, comparator, and outcome that need to be considered in future trials [47].

Applying evidence summarized in a systematic review to specific patients requires the same processes that are used to apply the results of individual controlled clinical trials to patients (see Chapter 18).

## Overviews and network meta-analysis

Overviews of systematic reviews are essentially an overarching review of all systematic reviews in a given topic. Also known as “umbrella reviews,” they emerged from The Cochrane Collaboration as a means of bringing together several separate reviews of different interventions for a particular condition. Such reviews may also include non-Cochrane reviews, and like a normal systematic review, quality assessment of included reviews and pooling of studies is performed, as was done in an overview of systematic reviews of prevention of atopic eczema [48].

*Network meta-analysis* within a systematic review refers to a form of meta-analysis whereby three or more treatments are compared directly using comparisons of interventions within randomized controlled trials and indirectly across trials based on a common comparator. In other words, if treatment A is compared with treatment B, and treatment B is compared with treatment C in a similar population, then it should be possible to make inferences about a comparison of treatment A versus treatment C since they have shared the same comparator. Such techniques are useful in at least three respects. The first is that they may provide essential data to guide health-care professionals or providers on how two new drugs that have only been compared against placebo compare against each other. The second is that they can inform ranking of efficacy of several drugs used for the same condition [49]. Finally, network meta-analysis provides a geometrical picture of which comparisons have been favored and which have been deliberately avoided in order to make certain drugs appear more effective than they really are [50]. Like any other study design, network meta-analysis has to be designed and conducted with rigor [51], and also has to consider the impact of reporting bias on the ranking of the various treatments included [52].

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## CHAPTER 9

# How to critically appraise a randomized controlled trial

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### The place of randomized controlled trials

The rationale and history of the randomized controlled trial is covered extensively in The James Lind Library ([www.JamesLindLibrary.org](http://www.JamesLindLibrary.org)), a nonprofit organization and free online resource that explains the development of fair tests in medicine. Although numerous examples of attempts at fair tests can be found, such as the controlled trial by James Lind in 1762 on the value of lemons in preventing scurvy for British sailors, many recognize the first well-documented randomized controlled trial (RCT) as that performed by the Medical Research Council on the use of streptomycin for the treatment of pulmonary tuberculosis in 1948 [1]. Many variants of clinical trials have developed since then, yet the basic principles of using concealed randomization as the fairest method of allocating study participants to an experimental versus control treatment and the blinded assessment of outcome has remained essentially the same. The RCT remains the most robust study to minimize the effects of bias when trying to assess the degree of effectiveness of a clinical intervention [2]. Yet, as with any study design, there are good and bad RCTs, and this chapter aims to guide the reader on how to tell them apart. As Naldi discusses in Chapter 10, RCTs are not the best source of study design to assess the potential harms of new treatments, especially for less common adverse effects [3].

It should be mentioned at the outset of this chapter that, as highlighted in Chapters 7 and 8, single RCTs should ideally be interpreted within the context of a high-quality systematic review of *all* relevant RCTs. The results of an isolated RCT, even when published in highly prestigious journals, can be hazardous when read in isolation. Thus, Ioannidis showed that of 49 original clinical research studies (almost all were RCTs) published in three major journals and cited over 1000 times, the effectiveness claims of around a third appeared to be exaggerated or contradicted by subsequent research [4]. Large treatment effects reported in initial small studies are especially hazardous, as effect sizes are shown to be smaller when additional trials are performed [5]. Such studies underline the notion that one RCT is seldom enough. The practicing dermatologist should aim to refer to high-quality systematic reviews as their first port of call for comprehensive evidence when available.

### Definitions of quality, validity, and bias

Quality, when referring to RCTs, is a multidimensional concept that includes appropriateness of design, conduct, analysis, reporting, and its perceived clinical relevance [6–9]. Validity refers to the extent to which the study results relate to the “truth.” Validity may be internal (i.e., are the results of *this* trial true?) or external (to what extent do the results of this trial apply to *my* patients?). Factors affecting external validity are discussed further in Chapter 18. It is no good starting to examine factors affecting external validity unless the reader is assured of the internal validity of an RCT – in other words, internal validity is a prerequisite for external validity.

Most readers will be familiar with the need to estimate the role of chance when interpreting results from RCTs. Once the basic lessons in interpreting *P* values and confidence intervals have been achieved, the role of chance as an alternative explanation of study results is usually an easy exercise, especially since such information is usually accessible in almost all published RCTs. In addition to assessing the role of chance, a crucial component in appraising the internal validity of a trial is assessment of its potential for bias. Bias denotes a systematic error resulting in an incorrect estimation of the true effect. Unlike the role of chance, which is usually explicit and well highlighted within RCT reports, the role of bias needs to be specifically searched for and assessed. With respect to clinical trials, bias may be best understood in terms of:

- Selection bias – resulting in an imbalance in treatment groups.
- Performance bias – treating one group of people differently from the other.
- Detection bias – biased assessment of outcome resulting from lack of blinding.
- Attrition bias – biased handling of deviations from the study protocol and those lost to follow-up.
- Selectively reporting outcomes bias – only reporting a selection of the outcomes.
- Publication bias – although *publication bias* (the tendency to conceal or delay publishing “negative” studies – see Chapter 8) is of great significance when it comes to assessing the effects of treatment during the conduct of systematic reviews of RCTs, I also mention it here because of its pernicious effects in distorting the

scientific record and because publication plans should be part of the design and conduct of all individual RCTs.

## How to tell a good dermatological randomized controlled trial from a bad one

### Quality criteria derived from research

Four main factors related to study reporting have been associated with altering the estimation of the risk estimate, usually by inflating the claimed benefit [8]. These are shown in Box 9.1, and are still considered today as the four most important indicators of RCT quality.

### Generation and concealment of treatment allocation

Generation and concealment of treatment allocation are two inter-related steps in the crucial process of randomization. The first refers to the method used to generate the randomization sequence. The second refers to the subsequent steps taken by the trialists to conceal the allocation of participants to the intervention groups from participants and those recruiting trial participants. Both aspects are designed to minimize selection bias, so that participants in a trial are allocated to one treatment or another on the basis of chance only.

Suggestions for adequate and inadequate definitions of the generation of randomization and subsequent concealment are shown in Box 9.2. Additional guidance is available in the *Cochrane Handbook* [10]. Studies that do not describe *how* the randomization sequence was generated should be viewed with some suspicion, given that humans frequently subvert the intended aims of randomization [11].

Concealing the allocation of interventions from those recruiting participants is a crucial step in the progress of an RCT. The randomization list should be kept away from enrollment sites (for

example, by a central clinical trials office or pharmacy). Internet randomization by a third party such as a clinical trials unit [12], whereby details of a new potentially eligible trial participant are entered irrevocably onto a trial database before an allocation code is offered, is another very secure way of concealing allocation. Less ideally, sealed opaque envelopes are used – a method that is still susceptible to tampering by opening the envelopes or holding them up against a bright light [11]. Failure to conceal such allocation means that those recruiting patients can foresee which treatment a patient is about to have. Such lack of concealment can result in selective enrollment of patients on the basis of prognostic factors [13], and loss of the critical “even playing field” that randomization was designed to achieve.

Motives for interfering with the randomization schedule include a desire on the part of investigators to ensure that their new treatment is successful by deliberately allocating patients in a better prognostic group to the new treatment. Another reason may be that a doctor wants to ensure that particular patients for whom they have sympathy are not allocated to a control or placebo group if their belief in the experimental treatment is high. Such selective recruitment is a form of selection bias, resulting in an unfair comparison of the interventions under evaluation. Trials in which concealment of allocation was judged to have been inadequate were found to have inflated the estimates of benefit by about 30% in comparison with studies reporting adequate concealment [8]. Although concealment of allocation may help with subsequent blinding of assessors and patients when recording outcomes, it refers to a process that occurs *before* participants enter the trial, and its prime purpose is to ensure that the groups to be compared are as similar as possible to each other. Whereas blinding of participants and assessors is sometimes not possible – for example, in some surgical procedures in which a sham operation might be considered unethical – concealment of allocation is *always* possible.

**Box 9.1** Factors to consider when assessing the validity of clinical trials in dermatology

#### The “big four” that should always be assessed

- Is the method of generating the randomization sequence and subsequent concealment of allocation of participants clearly described and appropriate?
- Were participants and study assessors blind to the intervention?
- Were all those who originally entered the study accounted for in the results and analysis (i.e., was an intention-to-treat (ITT) analysis performed)?
- Did the authors present the primary outcomes they planned to present or did they highlight only those outcomes that “looked good”?

#### Other factors worth looking for

- Did the study investigators use an adequate disease definition?
- Were the treatment groups similar with respect to predictors of treatment response at baseline?
- Were the outcome measures clinically meaningful to you and your patient?
- Did the investigators do an appropriate statistical test?
- Did the investigators test the right thing (i.e., between-group differences rather than just differences from baseline)?
- Have the authors misinterpreted no evidence of an effect as being evidence of no effect?
- Were the groups treated equally except for the interventions studied?
- Who sponsored the study? Could sponsorship have affected the results or the way they were reported?
- Is the trial clearly and completely reported?

### Blinding (masking) the intervention

Blinding or masking is the extent to which trial participants and others involved in the study assessments are kept unaware of treatment allocation. Blinding can refer to at least four groups of people: those recruiting patients, the study participants themselves, those assessing the outcomes in study participants, and those analyzing the results [14]. The term “double blind” traditionally refers to a study in which both the participants and the investigators are “blind” to the study intervention allocation, but the term is ambiguous unless qualified by a statement as to who exactly was blinded.

**Box 9.2** Adequacy of generation and concealment of randomization sequence

#### Generation of the randomization code

- Adequate: random numbers generated by computer program, table of random numbers, flipping a coin.
- Inadequate: quasi-randomization methods (for example, date of birth, alternate records, date of attendance at clinic).

#### Concealing the sequence from recruiters

- Adequate: if investigators and patients cannot foresee the assignment to intervention groups (i.e., numbered and coded identical sealed boxes prepared by central pharmacy, sealed opaque envelopes).
- Inadequate: allocation schedule open for recruiting physician to view beforehand, unsealed envelopes.

Blinding is less of an issue with objective outcomes such as death, but it is especially important with subjective outcomes such as the opinion of participants or assessment of disease activity, as often happens in many dermatology trials. Blinding may be achieved by a range of techniques, such as ensuring that placebo tablets look, feel, smell, and taste the same as the active tablets [15], or, in the case of ointments, by using the same vehicle or base in which the active ingredient is formulated [16]. Even outcomes that may at first seem very difficult to blind – such as parents' views on the effects of laser treatment versus observation only for their child's hemangioma – can be blinded by taking digital images and then asking a panel of independent parents to judge the therapeutic response whilst concealing the identity of the intervention groups [17]. Judging whether a study has been truly blinded can be tricky and relies on a clear description in the methods section of the steps taken to ensure blinding, such as the use of placebos. Just because a study is described as being “double blinded” does not necessarily mean that blinding was achieved. For example, placebo-controlled RCTs of oral retinoids (which have predictable adverse effects of mucosal dryness in nearly all those given the active drug) are impossible to blind effectively, despite studies regularly referring to them as “double-blinded” [18]. The same applies to controlled trials of topical capsaicin, which creates a burning sensation when applied to the skin [19]. Some trials test the effectiveness of their blinding methods by asking study participants at the end of the study to guess which treatment they had been allocated to [16].

In many circumstances, blinding of the intervention is not possible. As an example, in an RCT of ion-exchange water softeners for atopic eczema, participants could not be blinded as they could guess whether they had a genuine or sham water softener due to increased soap suds production [20]. In such situations, it is essential that the primary outcome measure for the trial is an objective one such as examination of the skin by a research nurse blinded to the allocation status. In this trial, there was no evidence of a treatment effect for the objective outcomes determined by blinded nurse assessors, but some evidence of treatment effect for subjective reports from the unblinded participants, underlining the importance of blinded outcome assessments [20].

It is important to emphasize the difference between allocation concealment and blinding, although they may superficially appear to be the same. Failure to conceal the randomization sequence may result in groups that are unequal in terms of severity or prognostic factors and is a form of selection bias, whereas failure to mask the intervention once a fair randomization has taken place represents a form of detection or information bias. Both can result in an incorrect estimate of the effects of a treatment. Studies that are not double-blinded typically overestimate treatment effects by about 14% in comparison with studies that are double-blinded [8].

### Accounting for all those randomized

The whole point of randomization is to create two or more groups that are as similar to each other as possible, the only exception being the intervention under study. In this way, the additional effects of the intervention can be assessed [21]. A potentially serious violation of this principle is the failure to take into account all those who were randomized when conducting the final main analysis – for example, participants who deviate from the study protocol, those who do not adhere to the interventions, and those who subsequently drop out for other reasons. People who drop out of trials differ from those who remain in them in several ways [22]. People may drop out because they die, encounter adverse events, get worse

(or no better), or simply because the proposed regimen is too complicated for a busy person to follow. They may even drop out because the treatment works so well. Ignoring participants who have dropped out in the analysis is not acceptable, as their very reason for dropping out is likely to be related in some direct or indirect way to the study interventions. Excluding participants who drop out after randomization potentially biases the results. For example, in a study of emollients for atopic eczema, the authors chose to only report the results of patients who did well and excluded patients who did poorly, thereby giving a more favorable impression of the treatment effect [23]. One way to reduce bias is to perform an ITT analysis, in which all participants initially randomized are included in the final analysis [22,24].

Unless one has detailed information on why participants dropped out of a study, it cannot be assumed that an analysis of those remaining in the study to the end is representative of those randomized to the groups at the beginning. Failure to perform an ITT analysis may inflate or deflate estimates of treatment effect [9]. Performing an ITT analysis is often regarded as a major criterion by which the risk of bias of an RCT is assessed.

It may be entirely appropriate to conduct an analysis of all those who remained at the end of a study (a “per protocol” analysis) alongside the ITT analysis, especially in trials that are designed to show therapeutic equivalence or noninferiority [25]. Discrepancies between the results of ITT and per-protocol analyses may indicate the potential benefit of the intervention in ideal compliance conditions and the need to explore ways of reformulating the intervention so that fewer participants drop out of the trial. Discrepancies may also indicate serious flaws in the study design. A good discussion of when and where it might be appropriate to exclude trial participants from the main analysis may be found elsewhere [26].

### Declaring and presenting the primary outcomes

Many trials report as many as 10 different outcome measures recorded at several different time points. Even by chance, at least 1 in 20 of such outcomes will be “significant” at the 5% level. It is therefore important to ensure that trialists of studies that use many outcomes are not data dredging. By data dredging, I mean performing repeated statistical tests for a range of outcome measures and then emphasizing only the one that “looks good” and that is statistically significant at the “magic” 5% level. Such a practice is akin to throwing a dart and drawing a dartboard around it. Instead of distorting evidence in this way, trialists should declare up front what they would regard as a single “success criterion” for a particular trial (i.e., the primary outcome measure). This way, the results are more credible if that main success criterion is fulfilled – as opposed to some secondary or tertiary outcome measure that turns out to be “significant” at one particular assessment time point.

In addition to data dredging in order to *highlight* the outcomes that look best, the phenomenon of selective reporting of outcome measures can also result in the deliberate *omission* of some outcomes that were part of the original study protocol. The issue of outcome reporting bias has been well documented by Chan and Altman in 519 trials with 553 publications relating to 10557 outcomes identified in trial protocols [27]. Chan, a dermatologist, found that on average, 20% of the outcomes measured in parallel group studies were incompletely reported, and that such incompletely reported outcomes had higher odds of being nonsignificant in comparison with fully reported outcomes (odds ratio 2.0; 95% confidence interval, 1.6 to 2.7). The medical literature, therefore, represents a selective and biased subset of study outcomes. Selective



**Table 9.1** Trial reporting and study quality may be related but are not necessarily the same. All poorly reported trials reside in the shaded area of uncertainty.

Reporting quality	Study quality	
	Good	Flawed
Clear	May be helpful for clinical practice.	At least you can tell it is flawed and make a judgment on utility.
Poor	A sparkling diamond – but how do you know?	Difficult to distinguish from a good but poorly reported study.

Source: Williams, 2010 [33]. Reproduced with permission from Biomed Central Ltd.

reporting outcome bias can be lessened by ensuring that all RCT protocols are registered in a publically accessible site and that the protocol includes a description of the main outcome measures [27–30]. In dermatology, one study of 109 RCTs on atopic eczema published between 2007 and 2011 found that only around one-third had been registered on an approved public register, and that only five trials provided enough information to be confident that reported outcomes were the same as the original registration [31].

**Quality scales**

Although space in journals has sometimes been suggested as a reason for not including vital information such as sample size calculation that could be found in original study protocols, it has been shown that faulty reporting generally reflects faulty trial methods [8,11,32]. The relationship between trial reporting and trial quality is illustrated in Table 9.1 [33].

A number of scales have been developed for assessing study trial quality over the past 20 years. These vary in the dimensions covered and in their complexity [7]. Generally, the recent trend has been to use the few quality criteria suggested in Box 9.1, plus a few more that the appraiser considers important in relation to the condition and question being studied [8]. It is now considered unwise to use summary quality scores in an attempt to “adjust” the potentially biased treatment estimate, because the effects of such adjustment vary with the scale used and the way in which the components of each scale are weighted [34]. Instead, greater emphasis is placed on using the *components* of the scale as The Cochrane Collaboration risk of bias tool, and then to consider how each aspect may affect the results [8,10].

**Additional empirical criteria**

**Disease definition**

Whereas it may seem simple to assess the four components of randomization generation/concealment, blinding, accounting for all those randomized with an ITT analysis, and comparing a trial protocol with what was eventually published in order to assess selective reporting outcome bias, other topic-specific items may need to be assessed in order to make sense of the value of a particular RCT. The influence of such disease-specific factors in dermatology is an area that requires further systematic research.

A clear description of the disease being studied may be important. For example, when referring to a child with atopic eczema/dermatitis, I would not trust a study that claimed a beneficial effect for a new treatment if the study included both children and adults with diverse eczematous dermatoses [35], as people with such conditions might respond differently [36]. And if the study did refer to atopic eczema/dermatitis, I would like to see a clear description of

how the disease was defined. Even disease subgroups may need to be defined – for example, a study seeking to reduce atopic eczema severity by reducing house mites might make little sense unless those included were shown to be sensitive to house dust mites in the first place.

**Similarity of groups for baseline differences**

In addition to helping to balance for the *known* predictors of treatment response, such as baseline disease severity (which could serve as confounders when evaluating treatment efficacy between groups), it has also been suggested that randomization will balance against unknown confounders [8]. This statement is superficially appealing, but is difficult to verify if these confounders are indeed unknown. Yet simple randomization, even when perfectly implemented on small sample sizes, may still result in imbalances in possible cofactors that can affect the treatment response. In other words, randomization is not a guarantee against imbalance, although more sophisticated methods of randomization, such as blocking, minimization, and stratification, can help minimize such imbalances [14].

It is quite common for the first table in the results section of an RCT report to show a long list of demographic characteristics of the participants in the different treatment groups, along with a statement to the effect that “the two groups did not differ statistically at baseline” [37]. Such a statement is problematic for two reasons:

- It is inappropriate to perform such multiple statistical tests without prior hypotheses – indeed, many of the variables recorded may be totally irrelevant to predicting treatment response.
- There may still be no arbitrary 5% statistically significant differences even for gross imbalances in treatment groups, simply because the groups are so small; that is, failure to demonstrate statistically significant differences between the groups may be related to lack of power.

Before reading such tables, the most important thing to do is to ask oneself beforehand, “What are the most important factors that may predict the treatment response?” and then to see whether they have been recorded. If there are major imbalances, such as in the baseline severity score, then these can and should be allowed for in a number of ways during analysis – for example, with a multivariate analysis adjusting for baseline severity as a covariate [14].

**“Sensible” outcome measures**

In evaluating a clinical trial, look for clinical outcome measures that are clear-cut and clinically meaningful to you and your patients [38]. For example, in a study of a systemic treatment for warts, complete disappearance of warts is a meaningful outcome, whereas a decrease in the volume of warts is not [39]. The development of scales and indices for cutaneous diseases and testing their validity, reproducibility, and responsiveness has been generally inadequate but is receiving more attention [40–42]. A lack of clearly defined and clinically useful outcome variables remains a major problem in interpreting clinical trials in dermatology. Usually, dermatology clinical trials need to include at least four outcomes: a patient-centered outcome that seeks the views of trial participants on the “success” or otherwise of the study treatments; an objective and validated outcome measure of treatment benefit that has not been tampered with; a measure of harm; and a validated quality-of-life scale.

Until better scales are developed, trials with the simplest and most objective outcome variables are probably the most useful.

Categorical outcomes are usually widely understood by clinicians and patients alike. Thus, trials in which a comparison is made between death and survival, patients with recurrence of disease and those without recurrence, or patients who are cured and those who are not cured are studies whose outcome variables are easily understood and verified. For trials in which the outcomes are less clear-cut and more subjective, a simple ordinal scale is probably the best choice. The best ordinal scales involve a minimum of human judgment, have a precision that is much smaller than the differences being sought, and are sufficiently standardized to enable others to use them and produce similar results [38,43]. There is currently an emphasis throughout the field of medicine to develop core outcome sets for clinical trials of a particular condition, an approach pioneered by the Outcome Measures in Rheumatology group (<http://www.omeract.org/>) and now encouraged by the international Core Outcome Measures in Effectiveness Trials group (<http://www.comet-initiative.org/>). In the field of dermatology, core outcome sets are being established, such as the Harmonising Outcomes for Eczema group (<http://www.homeforeczema.org/>), which has used international consensus techniques informed by evidence reviews to identify the four key domains that should always be measured in atopic eczema/dermatitis RCTs [44].

### Doing the wrong tests

It is quite common for continuous data such as acne spot counts to have a skewed frequency distribution. It may then be inappropriate to use parametric tests such as the Student *t*-test without first transforming the data. Alternatively, nonparametric tests that do not rely on the assumption of a normal distribution can be used. A quick way to check whether a continuous variable is normally distributed is to determine whether the mean minus two standard deviations is less than zero. If it is, the data are likely to be skewed. Continuous data are typically underspecified in terms of analyzing and presenting the full range of data in RCT reports [45].

### Testing the wrong thing

Performing a statistical test on something other than the main outcome of interest is a subtle but not uncommon error in dermatology trials [46,47]. When comparing a continuous outcome measure such as a decrease in acne spots between treatment A and treatment B, the correct summary statistic to challenge the null hypothesis of no difference between the treatments is to examine the *difference between the two treatments* in terms of the change in the spot count from baseline. Sometimes the investigators simply perform a statistical test on whether the acne lesion count falls from baseline in the two groups independently. If the fall in spot count reaches the 5% level in one group but not in the other, then the authors may conclude that “therefore treatment A is more effective than treatment B.” Perhaps the *P* value for change in spot count from baseline is 0.04 in one group (i.e., significant) and 0.06 in the other (i.e., conventionally nonsignificant). This practice is clearly inappropriate, since the difference *between* the two treatments has not been tested.

### Interpreting trials with negative results

Misinterpreting trials with negative results is a common error in dermatology clinical trials [48]. Failure to find a statistically significant difference between treatments should not be interpreted as showing that “treatment is ineffective.” Put another way, no evidence of effect is not the same as evidence of no effect [49]. In many dermatology trials, the sample sizes are much too small to detect

clinically important differences. Providing 95% confidence intervals around the main response estimates allows readers to see what kind of effects might have been missed. For example, in an RCT of famotidine versus diphenhydramine for acute urticaria, itch as measured by a 100 mm visual analog scale decreased by 36 mm in the famotidine group and by 54 mm in the diphenhydramine group, a difference of 18 mm (54 mm – 36 mm) in favor of diphenhydramine. Although the statistical test for this difference of 18 mm between the two treatment groups was not significant at the 5% level, there was a clear hint of a greater reduction in itch in the diphenhydramine group. The 95% confidence interval around the 18 mm difference between the groups was from –3 to 38 mm. In other words, the results were compatible with a difference of as little as 3 mm in favor of famotidine and as much as 38 mm in favor of diphenhydramine [50].

### The trial environment

Once randomized, it is important that the two intervention groups are followed up in similar ways. Previous studies have shown the nonspecific benefits of being included in a clinical trial, even in placebo groups [51]. Part of the benefit might be the result of better ancillary care and motivation prompted by frequent follow-ups and being “fussed over” by study assessors, a phenomenon known as performance bias [14]. Performance bias can be particularly problematic for talking therapies that involve groups compared with individual standard care, where it can be difficult to say whether the additional benefits found are due to the specific talking therapy or the extra attention afforded to those taking part in groups. It is important, therefore, to scrutinize whether the treatment groups have been treated equally in terms of the frequency and duration of follow-up and whether they have been afforded identical privileges except for the treatment under investigation. For chronic diseases such as atopic eczema, it is important to see whether additional “rescue” therapies are used that could confound the true difference between competing treatments. Recording and presenting data for co-treatments and adjusting for them are ways of evaluating their impact. Sometimes, especially in surgical trials, the effects of the expertise of the surgeon or center undertaking the procedure can result in an unfair estimation of treatment effect – a phenomenon that can be overcome by ensuring that participants are randomized to clinicians who are expert on delivering the intervention or by adjusting for “center effects” [52,53].

### Sponsorship issues

It is natural to assume that authors of a clinical trial of a dermatological drug that has taken years of development investment by a pharmaceutical company will strive to demonstrate that the drug is successful. Indeed, millions of dollars of profit may rely on convincing opinion leaders in dermatology of a new drug's worth. Yet the influence of sponsorship on efficacy claims has not been adequately explored in dermatology RCTs. Drug companies and trialists have many opportunities to influence journal readers when the results of their trial are published (Box 9.3).

Conflicts of interest are not unique to the pharmaceutical industry, although some of the best examples of distorting the scientific record have emerged from company-sponsored studies [54]. Those conducting trials for government agencies, for example, might have a vested interest in wishing to show that a new drug is less cost effective than standard therapy. Some independent clinicians with preformed conclusions about an existing treatment may be equally susceptible to being influenced by their own prejudices when

**Box 9.3** Ways to enhance the impact of positive studies or reduce the impact of negative studies

- Withhold “negative” trials from being published at all by keeping them as “data on file.”
- Delay release of such “negative” studies into the public domain.
- Stopping a trial early at a “random high.”
- Publish negative studies in an obscure or non-English-language journal.
- Deliberately select outcome measures that show the treatment in a better light – for example, Psoriasis Area and Severity Index (PASI) 50 instead of PASI 75.
- “Torture” the data by performing multiple statistical tests on subgroups.
- Use many statistical techniques until you find one that shows the results in the best light.
- Divert attention from the main “negative” findings by emphasizing biomedical markers and a mechanism of action smokescreen.
- Incorrectly interpret inconclusive studies as equivalence studies – for example, by suggesting that two drugs are the same when the confidence intervals surrounding their differences are large.
- Use a comparator that other studies have not used in order to avoid a head-to-head comparison with a current established treatment.
- Use the comparator drug at the wrong dose or frequency to show the active drug in a better light.
- Avoid mentioning significant adverse events in the abstract and discussion sections.
- Flood the literature with lots of placebo-controlled studies that make the new drug look impressive. Few doctors use placebos in clinical practice, and most would like to know how a new drug compares with the best existing active therapy.
- Use optimistic language and writing styles when discussing essentially negative studies – for example, repetition of positive results such as “nonsignificant trend in favor of,” or use percentage relative treatment benefits when the absolute degree of improvement is small.
- Publish positive study results in duplicate or triplicate – overtly or even covertly.

testing and writing up the results for that treatment. In assessing a study, readers should always consider who sponsored the study and ask themselves whether such sponsorship could have influenced the results or the way that they are presented. Empirical research from general medicine trials suggests that inclusion of a clear statement of pharmaceutical sponsorship does influence a clinician’s interpretation of results. Absence of declared sponsorship may not mean absence of sponsorship [55].

### Other factors

This short chapter can only touch on some of the bigger issues in interpreting clinical trials. For most of the chapter, I have referred to single pharmacological interventions. Other more complex interventions, such as educational classes for eczema families, consist of several defined components, such as the educational package itself, who delivers it, how it is delivered and reinforced, and so on, and may require additional special interpretation [56]. Guidance on the evaluation of RCTs of complex interventions is discussed elsewhere [57,58]. Trials are often divided into those that are explanatory and measure efficacy (can this intervention work under ideal trial conditions?) or pragmatic and measure effectiveness (how well does this intervention work when used under typical conditions?) [59], whereas in reality they lie on a pragmatic–explanatory continuum [60,61]. The reader is referred to other resources to learn more about variations in study design, such as adaptive designs, crossover studies, or internally controlled right/left limb studies, which are frequently used in dermatology [62].

Issues on the unit of randomization are relevant to some areas of dermatology, where the failure to consider the whole person as opposed to number of warts can have a distorting effect on trial conclusions [63].

### Attempts to overcome limitations in the conduct, reporting, and publication of clinical trials

At this point, the reader might despair at the many hazards in interpreting clinical trial reports and in the way that they have been published over the years. But nearly all of the issues described can and have been overcome by strict reporting guidelines and the compulsory registration of clinical trials. The need for better standards of reporting of trials have led to the Consolidated Standards of Reported Trials (CONSORT) statement, which was updated in 2010 [64]. CONSORT contains a structured checklist for reporting the details of clinical trials, including methods of randomization and concealment, blinding, ITT analysis, and a flow diagram to illustrate the progress of trial participants. Several dermatology journals now require that submitted clinical trial reports meet CONSORT standards in order to be published [28,65–67].

Whereas CONSORT may help with better reporting of trials that find their way into the public domain, it does not overcome the pervasive effect of publication bias [68]. The creation of prospective clinical trial registers accessible in the public domain is becoming a powerful tool to ensure that *all* trials are eventually published in some form, or at least that their presence can be determined by those doing systematic reviews of all available evidence [28–30]. Trial registers with fully accessible study protocols minimize publication bias, data dredging, and outcome reporting bias and reduce research wastage [69]. Publishing trial protocols in the public domain may also minimize the increasing problem of covert ghost authorship writing, which may occur in up to 75% of industry-sponsored trials [70]. Thankfully, several leading dermatology journals now require RCTs to have been registered in accordance with the International Committee of Medical Journal Editors statement [28,29,67]. The World Health Organization International Clinical Trials Registry Platform (<http://www.who.int/ictcp/en/>), holds an up-to-date record of trials registries that contain an internationally agreed set of information conforming to World Health Organization standards.

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# Assessing and explaining the evidence on harms of medical interventions

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## Introduction

Like other human activities, medical interventions can carry a risk of unintended adverse events. Whenever a drug is prescribed, it can potentially cause an adverse reaction. Despite limited accurate data, a widely cited meta-analysis of 39 prospective studies in US hospitals performed from 1966 to 1996 found an incidence of severe adverse drug reactions (i.e., life-threatening or prolonged hospital stay), among inpatients, of 6.7% and 0.32% deaths [1]. Despite these impressive figures, the rate of severe adverse reactions for any given drug is usually low. In addition, the system works in such a way that even a small increase in the incidence of a clinically severe reaction may prompt the withdrawal from the market of the implicated drug.

It is commonly stated that clinical decisions should balance the benefit with the risk, or more properly the harm, of the available options. A difficulty stems from the fact that data on benefits and harms of medical interventions are usually derived from different study designs and information sources. Our discussion focuses largely on the safety of drug use. While systems to survey the safety of medications are well established, that is not the case for other medical interventions (e.g., surgical procedures, invasive diagnostic tests). It is well accepted that no in vitro or animal models can accurately predict adverse events associated with a drug before it is used in humans. Advances in understanding of the causation of adverse reaction (e.g., pharmacogenomics) may one day make it possible to predict harms in individual patients more reliably [2,3]. An example of the way pharmacogenomics could influence the identification of high-risk people is provided by the association of Stevens–Johnson syndrome and toxic epidermal necrolysis with specific human leukocyte antigen haplotypes [4–8].

## Data sources

### The limitation of randomized clinical trials

Randomized clinical trials (RCTs) are very good for providing an unbiased estimate of treatment effect by controlling not only for determinants of outcome we know about, but also for those we do not know about. If RCTs demonstrate an important relationship

between an agent and an adverse event, then we can trust the results. However, RCTs are usually designed to document frequent events; that is, those associated with the intended effect of a treatment. With the usual sample size, which rarely exceeds a few thousand people, RCTs cannot accurately measure the frequency of uncommon events [9,10]. Besides the statistical power issue, additional limitations include the usual short duration of most clinical trials and the careful selection of the eligible population (restriction in patient selection according to age, co-morbidity, etc.). All in all, when an intervention has been proved effective in an RCT, its safety still remains to be established. At the very best, pharmaceutical companies may strive to work out the adverse effect profile of a drug before licensing, but because only a limited number of selected individuals can be exposed to the drug before it is released, only common adverse events can be accurately documented and the complete range of adverse events is left to emerge later. This is particularly true for delayed reactions and rare, but severe, acute events.

### The value of suspicion: case reports and case series

Unlike RCTs, individual cases or case series provide no comparison with a control group and cannot produce reliable risk estimates. Despite their limitations, astute clinical observations are still essential for describing new disease entities and raising new hypotheses concerning disease causation, including the effects of medical interventions [11]. Case reports remain a first-line modality to detect new adverse reactions after a drug has been marketed [12]. Spontaneous surveillance systems, like the International Drug Monitoring Programme of the World Health Organization (WHO), capitalize on the collection and periodic analysis of spontaneous reports of suspected adverse drug reactions [13]. All physicians and other health workers and also patients are expected to take an active part in promoting the safety of medical interventions and to contribute by reporting any suspected adverse events they observe in association with drug use [14]. Collections of reported adverse events may be explored to raise signals (Table 10.1) to be validated by more formal study designs; that is, studies providing estimates of incidence rates and quantifying risks [15,16]. Spontaneous

**Table 10.1** Criteria for signal assessment in spontaneous surveillance systems.

1	Number of case reports
2	Presence of a characteristic feature or pattern and absence or rarity of converse findings
3	Site, timing, dosage-response relationship, reversibility
4	Rechallenge
5	Biological plausibility
6	Laboratory findings (e.g., drug-dependent antibodies), data from animal toxicology
7	Previous experience with related drugs

reporting should be seen as an early warning system for possible unknown adverse events; it is prone to many kinds of bias [17]. Case reports may be more effective in revealing unusual or rare acute adverse events. In general, they do not reliably detect adverse drug reactions that occur widely separated in time from the original use of the drug or that represent an increased risk of an adverse event that is common in populations not exposed to the drug. One concern with spontaneous reporting systems is that they are hindered by low reporting rates, and when adverse reactions are reported the information is of variable quality.

### Epidemiological studies: the most comprehensive source of data

Quantitative estimates of harms associated with drug use may be obtained from analytic epidemiology studies – that is, cohort and case-control studies [18] – and from a number of modifications of these traditional study designs pertaining to the broad area of pharmacoepidemiology (Table 10.2). These observational (nonrandomized) studies are prone to unmeasured confounders and biases and provide less-stringent results than RCTs. On the other hand, in the “real world,” these study designs may represent the only practical way of obtaining risk estimates once a new drug has entered the market. Cohort studies are studies where groups are defined according to the exposure status (e.g., users and nonusers of a drug) and are followed up with subsequent events being recorded and compared [19,20]. In contrast, case-control studies are studies where groups are defined according to their experience of an outcome of interest (e.g., cases of toxic epidermal necrolysis and their adjacent controls) and prior exposures are ascertained retrospectively and compared [21]. A crucial point for the validity of a case-control study is the choice of appropriate controls. In principle, controls should be an unbiased sample of those individuals composing the so-called “study base.” Controls for cases arising in the ambulatory population with resultant hospitalization (community cases) may be represented by patients admitted to the same hospitals as cases for an acute condition or for an elective procedure not suspected of being related to drugs [22].

Generally speaking, cohort studies are better suited to the study of rare exposures and common events, and case-control studies to the assessment of rare outcomes and relatively common exposures. In addition, while cohort studies allow the assessment of several outcomes for one specific exposure, case-control studies can assess the role of a range of different exposures on the development of a single, specific outcome. Cohort studies are not feasible when dealing with rare events, because millions of drug users have to be observed for years. In these conditions, case-control studies with a very large population base are the most feasible methods. For example, intuitively, only a case-control study would be feasible to assess the pharmacological risk for a disease like toxic epidermal necrolysis with an expected rate in the general population of one case per million people per year [23,24].

**Table 10.2** Examples of pharmacoepidemiologic methods.

- Intensive hospital monitoring
- Prescription-event monitoring (PEM)
- Cohort studies (linked or not to registries)
- Case-control studies and case-control surveillance
- Case-crossover design
- Nested case-control studies
- Record linkage

**Table 10.3** Measures of association.

Patients	Adverse event (cases)	No adverse event (controls)
Exposed	<i>a</i>	<i>b</i>
Not exposed	<i>c</i>	<i>d</i>

Relative risk =  $[a/(a + b)]/[c/(c + d)]$ .

Odds ratio =  $(a/c)/(b/d)$ .

Excess risk =  $[a/(a + b)] - [c/(c + d)]$ . Excess risk may be also referred to as the “risk difference” or the “absolute risk reduction.”

NNT =  $1/\text{Excess risk}$ .

NNT from case-control studies =  $1/[(\text{Odds ratio} - 1)(\text{Unexposed event rate})]$ .

It is important to measure outcome and exposure in the same way in the groups being compared in observational studies. On the other hand, even if investigators document the comparability of potential confounding variables in the groups being analyzed (exposed and nonexposed cohorts, or cases and controls) or use statistical techniques to adjust them, there may be an important imbalance that the investigators do not know about or simply have not measured that may be responsible for any observed difference. This is the main limitation of observational studies compared with RCTs. It is usually considered that such analytical studies should be developed with the aim of testing a specific predefined hypothesis. In the last few decades, modifications of traditional cohort and case-control studies have been developed to explore new associations and to raise signals. Record linkage is based on linkage of data on exposure and outcome from large electronic databases, while case-control surveillance is the ongoing collection of cases of pre-specified rare and severe acute events and of suitable controls to look for new associations of the events with drug exposure [25].

The association of an exposure with a given event is usually expressed in terms of a relative risk or odds ratio (an estimate of the relative risk obtained from case-control studies) (Table 10.3). The relative risk is a measure of the size of an association in relative terms. It refers to the ratio of the incidence of the outcome among exposed individuals to that among nonexposed. Values  $>1$  represent an increase in risk associated with the exposure, while values  $<1$  represent a reduction in risk. A relative risk of 2, for example, tells us that the event under study occurs twice only in the exposed people as in nonexposed. For rare events, even a large relative risk may translate to the occurrence of a few additional drug reactions. The total incidence of an outcome among exposed persons is a combination of the baseline incidence plus the excess of incidence due to the exposure. The excess risk (or risk difference or absolute risk reduction) is calculated as the difference between the incidence among exposed individuals and the incidence among nonexposed individuals. It measures the occurrence of an outcome among exposed individuals that can be attributed to the exposure. As such, it is a better measure of the impact of different outcomes than the relative risk, and a more informative measure from a physician's and a public-health point of view. Measures of excess risk are directly calculated in cohort studies and, provided that data on the



incidence of the outcome are available in the underlying unexposed population, they can also be derived from case–control studies.

### A trend toward changing the surveillance paradigm: proactive pharmacovigilance

In recent years, the progression of evidence from unsolicited case reports to more formal epidemiological studies has been partly blurred by the emergence of the concept of “proactive pharmacovigilance,” which involves the a-priori identification of important areas of uncertainty about safety and the implementation of studies aimed at reducing these uncertainties, ideally as soon as a drug has entered the market [26]. One example of such an attitude is the already mentioned mechanism of case–control surveillance where rare and severe acute events frequently associated with drug use are examined for their associations with specific etiologic candidates via a case–control design [25]. Another example involves data mining and signal detection by scanning large databases that may be interconnected (record linkage) [27]. A further example is offered by population-based treatment registries, where registration and follow-up of patients being prescribed predefined drugs of interest occur [28]. If organized in a similar way, data from registries considering the same drugs could be merged to obtain summary estimates of risks for adverse events of interest [29,30]. Recently, the European Medicines Agency introduced Risk Management Plans, and is promoting proactive pharmacovigilance with the development of the European Network of Centres for Pharmacovigilance and Pharmacoepidemiology [31].

### Back to the individual patient

What is the risk of extraspinal hyperostosis in a psoriasis patient treated for several months with acitretin? Does psoralen+UVA therapy increase the risk of non-melanoma skin cancer in a patient being treated for mycosis fungoides? What is the chance of severe depression in an adolescent on 13-*cis*-retinoic acid for acne? To address these questions, physicians must effectively search for evidence and be able to assess the validity of the available data, to consider the strength of any documented association, and its relevance to an individual patient [32].

We have already noted that many different sources of information should be looked for and the search should not be limited to RCTs [33]. When data from RCTs are scrutinized, the statistical power to rule out any important adverse event should be taken into account. When dealing with observational studies, it should be carefully considered if they provide reliable quantitative risk estimates or simply generate signals needing further validation. The optimal study design should be one assuring unbiased comparison between exposed and unexposed groups. Comparison groups should be similar with respect to important determinants of outcome. Outcome and exposure should be measured in the same way in the groups being compared, and the exposure should clearly precede the adverse outcome. In addition, follow-up should be sufficiently long and complete and the study should have enough statistical power to document the association of interest.

When risk estimates from several studies are available, are they roughly in the same direction or are they consistent? If not, reasons for the discrepancies should be looked for. Systematic reviews may help to summarize the study results [34]. Unfortunately, meta-analyses of observational studies are of less value than those of RCTs [35]. Once an association has been established, the magnitude of the risk should be taken into account and expressed in

**Table 10.4** Discussing benefits and harms with patients, and monitoring treatment.

- 1 Start with the aims of treatment, for each option considering specific benefits and harms, their intensity and likely duration, how likely they are to occur, and what we do not know about it
- 2 Find out how much the various possible outcomes matter to the patient
- 3 Jointly make the choice, decide when and how to follow up and review the treatment, and what you will want to know then
- 4 Consider when to change the dose, and how to decide when to stop the drug
- 5 Monitor treatment over time, asking a few questions:
  - How is the patient using the drug?
  - Is it still needed? Is it still working sufficiently?
  - What does the patient say about the drug?
  - Has anything unexpected happened? Might it have to do with the drug? If so, consider reporting it (by relying on local spontaneous reporting system)

Source: Herxheimer, 2005 [39].

understandable terms if they are to help clinicians. We have already noted that, from the perspective of a physician, the excess risk (or risk difference) is more informative than the relative risk. In the context of RCTs, Sackett and co-workers proposed a method for converting risk differences into a more intuitive quantity, *the number needed to treat* ( $NNT = 1/\text{excess risk}$ ) [36]. It is the number of people who must be treated in order that one clinical event is prevented by the treatment at issue (e.g., the number of people to be treated to avoid one patient experiencing a relapse of psoriasis). The “number needed to harm” (NNH) or “number of patients needed to be treated for one additional patient to be harmed” (NNTH) [37] is the number of people exposed to a given treatment such that, on average and over a given follow-up period, one additional person experiences an adverse effect of interest because of the treatment. In RCTs and cohort studies, NNH is directly calculated as the reciprocal of the excess risk. Recently, a formula has been proposed using odds ratios from case–control studies and data on the event rate in the unexposed population (Table 10.3) [38]. According to the formula, giving an odds ratio of 3 and unexposed event rate of 1 per 1 000 000 people, the NNTH can be calculated as 500 000 (i.e., 500 000 people to be treated to experience one additional adverse effect with the treatment).

After deriving estimates for the potential harm of an intervention, they should be weighed against the expected benefits of the same intervention. The adverse consequence of not withholding the possible harm from using the intervention should be carefully considered. A final decision should try to integrate probability issues with the patient’s values and preferences about therapy. This requires patient education about the benefits, possible harms, and risks of alternatives tailored to the particular patient’s risk profile and communication skills by physicians [39].

To conclude, not only should physicians be able to retrieve and critically assess the evidence on the safety of any given intervention, but they should actively promote safety by contributing to surveillance programs once an intervention is proposed to the medical community, and should be able to effectively communicate benefit and harms to individual patients, enabling them to share therapeutic decisions and improving treatment adherence and effectiveness (Table 10.4).

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# How to evaluate diagnostic tests

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## Introduction

Every patient encounter involves a diagnostic process that establishes, confirms, or refutes a diagnosis. In some cases in dermatology this process is often simply examination of the skin. In other cases dermatologists use the full range of diagnostic tests available in medicine to confirm or establish a diagnosis. Within this range of options the choice of diagnostic tests depends on many factors, including:

- 1 the relative likelihood of the competing diagnoses;
- 2 the seriousness and therapeutic implications of the alternative diagnoses (e.g., is there a diagnosis that may be unlikely, but serious enough that it cannot be missed?);
- 3 the costs, toxicity, and difficulty of treatments;
- 4 the ability of distinguishing among the diagnoses with the diagnostic tools available;
- 5 the price and availability of the test;
- 6 the risks and discomforts associated with the test.

Tests are used when it is expected that the test can differentiate between the diseases in question. For example, a biopsy may not be used to distinguish between most generalized viral and drug eruptions because the histopathology of both entities is very similar. Instead, the history of concurrent symptoms or of recent drug exposure may lead to a diagnosis or suggest that viral titers be drawn. Ideally, a test will either confirm a diagnosis and lead to initiation of treatment, or exclude it.

## Critical appraisal of diagnostic studies

### Quality of evidence

To be valid, studies of diagnostic tests should have certain minimum features (Table 11.1). The test should be compared with a criterion or “gold” standard and the comparison should be blinded. The criterion standard needs to be consistently applied, and the study has to be conducted in an appropriate population. More detailed but important information that needs to be reported in studies evaluating tests has been published and will be helpful to assist the informed reading of the literature [1,2].

Studies reporting diagnostic tests in dermatology should adhere to established international reporting standards [1,2]. Studies of

diagnostic tests are prone to bias like other trials, but the type of design-associated flaws that influence performance characteristics is different from therapeutic trials. Many of these problems stem from the need to subject all patients to an often invasive or expensive gold standard in order to establish a diagnosis. Failure to do so in a wide range of patients often leads to overestimation of the test’s accuracy because, even for those patients for whom the probability seems low, the gold standard test identifies cases that may have been missed by other tests [3].

As in all types of study design, the results of diagnostic studies depend significantly on the population that is studied. A relevant group of patients and adequate population to study a test is defined based on the similarity of the spectrum of the disease in the study population to the population in which the test will be used. Reported performance measures of a test may differ by up to a factor of 3 in different clinical settings, depending on the patient case-mix (i.e., prevalence and severity of disease). This effect is called the spectrum effect [4]. Results from diagnostic studies cannot be generalized beyond the spectrum of the population that was studied.

Ideally, investigators should study a consecutively recruited population with a wide range of disease presentation. Many diagnostic studies, however, suffer from the problem that the gold standard is an invasive test (e.g., a skin biopsy). In order to avoid this test in patients who are not likely to have the disease, more severely affected patients are recruited and assessed. This recruitment bias may enhance the performance measures of the test, in that it skews the population toward a clinically obvious group.

Some investigators choose systematically not to subject patients with low probability and negative tests to the gold standard. These investigators will miss less obvious cases and overestimate the test performance. A variation of this is the differential verification bias, where a less rigorous reference standard is used for these patients. Test and reference standard need to be evaluated independently and blindly. Test accuracy may be overestimated by up to 30% if independent and blinded evaluation is not performed [4].

### Indices of test accuracy

The results of diagnostic studies are reported as one or more indices of test accuracy that describe the performance or operating characteristics of the test (Table 11.2). A highly specific test rules in the

diagnosis when positive, and a highly sensitive test can rule out the disease when negative. It is far from clear how high the sensitivity or specificity of tests has to be in order to reliably rule in or out a disease. Most authors would say greater than 0.95.

The positive and negative likelihood ratios, pretest probability, posttest probability, and threshold for action are important con-

cepts that must be understood to determine whether the results of a paper describing test characteristics are clinically relevant. The positive likelihood ratio is the percentage of people with the disease who have a positive test divided by the percentage of people who do not have the disease but who have a positive test. One way to calculate the likelihood ratio is sensitivity/(1 – specificity). The positive likelihood ratio estimates how much higher the likelihood of the disease is, given a positive test (posttest probability), compared with the probability before the test is done (pretest probability). Thus, it estimates the value of the test in informing the clinical decision.

The negative likelihood ratio is the index to calculate how much more likely a disease is going to be absent given a negative test. The likelihood ratio negative is the percentage of people with the disease

**Table 11.1** Quality of evidence in a study of a diagnostic test.

1. Independent, blind comparison with a reference (“gold”) standard of diagnosis
2. Evaluated in an appropriate spectrum of patients (like those in whom it would be used in practice)
3. Consistent application of the reference standard regardless of the diagnostic test result
4. Blinded evaluation of reference and test standard

**Table 11.2** Performance parameters for diagnostic tests. Source: Scott *et al.*, 2008 [3]. Reproduced with permission of Wiley.

		Target disorder		
		Present	Absent	Totals
Diagnostic test	Positive	A	B	A + B
	Absent	C	D	C + D
	Totals	A + C	B + D	A + B + C + D
Test characteristic	Alternative name	Question addressed	Formula and calculation	
Prevalence	Pretest probability	How common is the disease in the test population?	$(A + C)/(A + B + C + D)$ Patients with target disorder/all patients	
Sensitivity	True positive rate	What is the proportion of patients with the disease that have a positive test?	$A/(A + C)$ Patients with the target disorder and positive test/all patients with the target disorder	
Specificity	True negative rate	What is the proportion of patients without the disease who have a negative test?	$D/(B + D)$ Patients without the target disorder and a negative test/all patients without the target disorder	
Positive predictive value	Posttest probability of the disease with a positive test	What is the probability of the disease if the patient has a positive test?	$A/(A + B)$ Patients with a positive test and the disease/all patients with a positive test	
Negative predictive value	Posttest probability of health (no disease) with a negative test	What is the probability of no disease with a negative test?	$D/(C + D)$ Patients with a negative test and without the disease/all patients with a negative test	
Diagnostic accuracy		What proportion of all tests has given a correct result?	$(A + D)/(A + B + C + D)$ All patients positive test and with the disease (true positives) and all patients with a negative test who did not have the disease (true negatives)/all patients	
Likelihood ratio of a positive test (positive LR)		How much more likely is a positive test to be found in a patient with the disease than in a patient without the disease?	$[A/(A + C)]/[B/(B + D)]$ True positive rate/false positive rate, or [patients with positive test and disease/all patients with positive tests]/[patients with positive test without the disease/all patients without the disease], or rearranged to sensitivity/(1 – specificity)	
Likelihood ratio of a negative test (negative likelihood ratio)		How much more likely is a negative test to be found in a patient with the disease, than without the disease?	$[C/(A + C)]/[D/(B + D)]$ False negative rate/true negative rate, or [patients with a negative test with the disease/all patients with the disease]/[patients with a negative test and without the disease/all patients without the disease], or rearranged to (1 – sensitivity)/specificity	
Diagnostic odds ratio		How much more likely is the test to make a correct diagnosis than an incorrect diagnosis in patients with the disease?	Ratio of the positive likelihood ratio/negative likelihood ratio, or rearranged $(A \times D)/(B \times C)$	
Number needed to diagnose		How many patients have to be tested to give one correct positive test? (Primarily used for the evaluation of screening tests)	$1/\text{true positive rate} - \text{false positive rate} = 1/\text{sensitivity} - (1 - \text{specificity})$	

who have a negative test divided by the percentage of people who do not have the disease who have a negative test. The likelihood ratio negative is  $(1 - \text{sensitivity})/\text{specificity}$  and provides estimation of how much lower the likelihood of the disease is, given a negative (posttest probability), compared with the probability before the test is done (pretest probability). Whereas likelihood ratios concern the test performance in patients with or suspected to have the disease, the predictive values will assess the probability of the disease in patients with a positive test, or absence of disease in a patient with negative test (see Table 11.2 for details).

An ideal test is one that will almost always be positive when the disease is present and negative when the disease is absent. Thus, it has high sensitivity and specificity. Such a test would have a very high positive and a very low negative likelihood ratio [5].

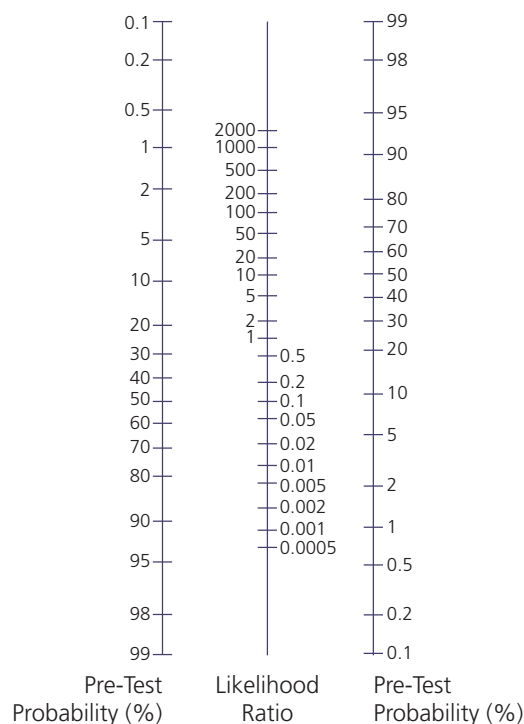
However, even tests with good characteristics fail if the population being tested has a very high or very low prevalence of disease. A very specific test fails if used in groups of patients who have a very low probability of the disease. If there is little chance of finding a sick patient in a group, a very specific test may have a larger number of false positives than true positives. Similarly, a very sensitive test may have a seemingly large number of falsely negative results if used in a population with a high prevalence of disease. The lower the prevalence of disease in a tested population, the more confident we can be that a negative test indicates the absence of the disease, but the less confident we can be that a positive test indicates the presence of diseases. For example, in a group of 1000 healthy patients, a test with a specificity of 95% will identify 50 patients as diseased who are not diseased. Tests are most useful or predictive when the disease prevalence or pretest probability hovers around 50% [4].

Overuse of tests leads to follow-up tests and potentially overdiagnosis. While the costs to the health system associated with overtesting have been given some attention, the human costs in terms of disruption of life, anxiety, and risks associated with the tests are equally, or even more, important.

For the likelihood ratio to be useful, it is important to understand pretest probability, posttest probability, and threshold for action. Pretest probability is an estimate of how likely it is that the patient has the disease before the test is done. The pretest probability is based on available published data like the prevalence of the disease in a population, or based on physician experience and judgment. While prevalence data may give some indication, most testing in dermatology is based on clinical findings, which increase the pretest probability beyond the prevalence of the disease. Judgment, which may incorporate the likelihood of the competing diagnoses, is needed.

Once the pretest probability is known or estimated and the likelihood ratio is determined, a nomogram can be used to estimate the posttest probability (Figure 11.1). If the nomogram is not available, the calculations can be done manually, but require conversion of probabilities to odds. For a defined group of individuals or patients the odds of disease are defined as the probability of having the disease divided by the probability of not having the disease, or the probability divided by one minus the probability:  $\text{odds} = \text{probability}/(1 - \text{probability})$ .

For example, if in a similar group of patients the probability of a disease (or the proportion of people with the disease) is 0.60 (60%), the odds of the patients having the disease are  $0.60/(1.0 - 0.60)$ , or 3:2 (1.5) in that group. The posttest odds equals the pretest odds multiplied by the likelihood ratio. The formula  $\text{probability} = \text{odds}/(\text{odds} + 1)$  is used to convert odds back to probability. In our



**Figure 11.1** Nomogram for determining the post-test probability. To determine the post-test probability, draw a straight line through the pre-test probability and the likelihood ratio and read the post-test probability on the right.

example, if the patient has a positive test and the test has a likelihood ratio positive of 10, their posttest odds are 15 (15:1). The posttest probability of having the disease would then be  $15/(15 + 1) = 0.94$  or 94%.

Tests with likelihood ratios close to one are not likely to significantly change the posttest probability from the value of the pretest probability, since the pretest probability multiplied by one or a factor close to one results in a posttest probability of the same or nearly the same value. These tests are not helpful because they are unlikely to move the pretest probability above the threshold of action.

The threshold of action is the certainty that is needed to establish the diagnosis and act on it. The threshold of action depends on the clinical situation and the test. For clinically obvious and recurrent tinea pedis, for example, the threshold of action (i.e., prescribing a topical antifungal) will be low and the practitioner may decide to treat without performing any test. A negative skin scraping would not change the treatment decision in this case. For a patient suspected to have mycosis fungoides, however, a number of biopsies may be needed until a diagnosis is established, because histological confirmation is essential to establish this serious diagnosis. Thus, there are different thresholds for action for initiating treatment and making a diagnosis in different clinical situations.

### Applying evidence about a diagnostic test to the care of individual patients

The key questions to ask to determine whether the results of a diagnostic study can be applied to a specific patient are shown in Table 11.3.



**Table 11.3** Can you apply the evidence about a diagnostic test in caring for your patient?

- 
- Is the diagnostic test available, affordable, accurate, and precise in your setting?
  - Can you generate a clinically sensible estimate of your patient's pretest probability (from practice data, from personal experience, from the report itself, or from clinical judgment)?
  - Will the resulting posttest probabilities affect your management and help your patient? (Could it move you across a test-treatment threshold? Would your patient agree to the test and treatment?)
  - Would the consequences of the test help your patient?
- 

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# What makes a good case series?

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## Introduction

Case reports and case series are often the first available evidence for the effectiveness of a treatment or for rare adverse effects of interventions. The British National Institute of Clinical Excellence (NICE) relies on evidence from case series in 30% of its reports that cover all fields of medicine. In spite of their methodological shortcomings, an analysis of case series in two areas relevant to NICE did not find that outcomes were better in the case series than in randomized controlled clinical trials of the same interventions [1]. Indeed, case series can generate high-quality evidence even without a documented control group, when the rates of events in a control group are likely to be near zero. This is most often the case when reporting of adverse events. These adverse events are not observed in the control group (e.g., those not taking medication) [2]. In our experience, the case reports and small series in dermatology have different characteristics and fairly often promote likely ineffective treatments with exaggerated conclusions [3]. However, they may remain the only evidence for the effectiveness of a treatment if controlled clinical trials are not available [4]. In dermatology, the most common reasons that controlled clinical trials may not be available are reasons of necessity, feasibility and of scale.

**Necessity.** The first and most obvious reason for lack of clinical trials is that treatments are so clearly effective that controlled clinical trials seem unnecessary (e.g., the use of insulin for type I diabetes) [5]. Such “all or none” treatments are acknowledged to have achieved the highest level of clinical evidence even without randomized clinical trials. All-or-none conditions are met when all or most patients died before the treatment became available, but some or many survived on treatment; or when some patients died before the treatment became available, but none or few died on it [6]. This “all-or-none” effect is exceedingly rare in dermatology, but the use of systemic corticosteroids in pemphigus vulgaris may fall in this category.

**Feasibility.** Studies that challenge the clinical perception of participants can be very difficult or impossible to conduct, because participation and recruitment of patients cannot be achieved. If therapies are strongly believed to work, there is most likely little interest to fund or conduct trials into their effectiveness. This state of affairs is unfortunate because the history of medicine is full of

reports of established practice that were ineffective or even harmful when subjected to clinical trials.

**Scale.** In dermatology there are treatments for more than 2000 syndromes or diseases. Many of these diseases are so uncommon that trials would have to be multicentered and very expensive. Finding funding for such studies on rare skin disorders to be conducted across several countries is often impossible, and pharmaceutical companies have almost no financial incentive to develop new drugs for rare diseases. Many treatments in dermatology are not very good and have low response rates which inflate the study sizes needed to demonstrate clinically meaningful and statistical differences. It therefore seems likely that many skin diseases and their treatments will never be subjected to clinical trials for pure questions of scale. In dermatology, the majority of diseases are unlikely to be the object of primary licensing trials. Thus, for a long period, or indeed forever, the only evidence for newly licensed drugs available comes in the form of case series or case reports. When reading this book it becomes obvious that for these reasons case series remain important clinical evidence in dermatology because they are often the only source of available evidence.

Recently, there has been renewed interest in the methodology of case reporting. Guidelines for the reporting of primarily therapy-oriented case reports have been developed and their publication as case reporting guidelines is imminent; this checklist should be helpful for authors and reviewers alike (J.J. Gagnier and D. Riley, personal communication, April 21, 2013). Another initiative has been the attempt to distinguish case series from cohort studies. The authors of a recent paper that separates the two designs argue that the difference between a case series and a cohort study is the ability of the latter to generate absolute risks [7]. Based on this assessment, the authors define case series as outcome based. By this definition case series are investigations in which patients with a certain outcome and a usually common exposure (disease or intervention) are described. Another type of case series is the description of a number of patients with their clinical characteristics, either as a prevalence study to describe or as a series of incidence cases in rare diseases. This separation of case series from cohort studies based on their statistical utility is intuitively convincing. It is also correct that the small number of case series cannot be the sole

distinguishing factor from cohort studies from a methodological point of view, but this differentiation creates the new problem that the number of cohort studies becomes inflated. It now includes often haphazard collection of poorly described individual cases that populate the literature. The authors acknowledge this problem and reasonably point out that the calculation of risks is not wise, even if it is possible, in a poorly conducted or reported cohort study. For therapeutic studies, they point out that a comparison group is almost always needed. We will avoid this differentiation; rather, in this chapter, we will focus on case series that may have many of the characteristics of cohort studies, but are either too small to calculate risks with confidence intervals small enough to be meaningful or too poorly reported to make use of statistics a good idea. In our opinion, this group covers the overwhelming majority of what has been traditionally thought to be case series in dermatology.

## Methodology of case series

Some characteristics of good case series are traditional methodological features associated with clinical trials (Table 12.1). In general, as for clinical trials, it is essential that the report allows full understanding of what happened to the patients. The ideal case series for the reader is one which constitutes an uncontrolled clinical trial and is ideally preplanned with blinded outcome observations. These trials are rare, however, because the majority of case reports in dermatology are published as consecutive cases of patients who have failed standard treatment. Usually, the treatment is compassionate and thus not usually administered according to a standard protocol.

The purpose of this chapter is to delineate the characteristics of high-quality case series, always keeping in mind that Phase III, randomized controlled clinical trials may never come. Whereas there is little literature, there is some on how to improve case reporting and case series: papers by Moses [5] and Abel [8] and

most comprehensively M. Jenicek's book *Clinical Case Reporting in Evidence-Based Medicine* [9]. The recommendations offered in this chapter rely heavily on this literature, which in essence uses the experience gained with cohort studies to improve case reports.

## Diagnosis

The authors of any case report or case series must explicitly state the diagnostic criteria used to establish the diagnosis of each patient reported so that others wishing to replicate the study may do so with similar patients. The diagnostic criteria may include histological confirmation, which should also be described in detail. Appropriate testing to exclude other entities in the differential diagnosis should be performed and reported.

## Inclusion and exclusion criteria

At the core of any description of case series is the delineation of exclusion and inclusion criteria. These criteria are often important to understand the clinical reasoning of the authors. They help the readers to apply the findings of the series to their patients and to define the external validity and generalizability of the findings, as they delineate the population to whom the observations are applicable. Inclusion and exclusion criteria are often used to increase the power of clinical trials by restricting studies to populations of patients who are most likely to respond based on their age, stage of the disease, or lack of concomitant diseases. While these selection criteria are likely to improve the outcome of any treatment, they introduce selection bias and seriously reduce the external validity of the study.

Detailing exclusion criteria can help to assure clinical safety, in that they describe who should not get the treatment in question. For example, patients with renal failure, children, or pregnant women may need to be excluded. The treatments that need to have failed before the experimental treatment is tried should be specified. Implicit inclusion and exclusion criteria are even helpful and illustrative in case reports, where they help the reader to identify the patients that the authors think due to theoretical considerations or knowledge about the side-effect profile of the therapy are not suitable for this therapy.

## Informed consent

Case reports and series are often the result of compassionate use rather than preplanned clinical trials. For the latter, informed consent and institutional review board (IRB) approval are required. IRB approval is not mandatory for compassionate use, but informed consent needs to be sought from the patient for any novel treatment. IRB approval indicates that the series has been collected prospectively, which is likely to signal higher quality by potentially reducing the selection bias that is likely in retrospective trials. That informed consent was obtained should be documented. As in any treatment, the authors should note that they have explained the risks and benefits and particularly the experimental nature of the treatment to the patients and that they have consented.

## Consecutive cases

The greatest threat to the credibility of case series is uncontrolled selection bias. Therefore, all consenting, eligible patients at an institution or under the care of one physician should be included in the

**Table 12.1** Methodology of case series.

Diagnosis	Are the diagnostic criteria clearly identified, and met by the patients included in the series?
Inclusion and exclusion criteria	Are inclusion and exclusion criteria clearly stated?
Informed consent	Has the patient consent been documented? For prospective studies: is IRB approval documented?
Consecutive cases	Are all consecutive patients treated by one physician or at one institution included?
Natural course of the disease	Is there any reference to the natural course of the disease, or, if applicable, the course on standard treatment?
Dosages	Are the treatments' dosage, duration, and titration described adequately?
Outcome measures	Are the outcomes of the therapy well defined and clinically relevant?
Patient perception	Is there any documentation of the patient's perception of the outcome of treatment?
Safety	Do the authors explain the toxicology and safety issues associated with the treatment? Do they abstain from unfounded claims about safety?

series. Feinstein pointed out rather elegantly that even this approach has inherent limitations, since the patient introduces bias by choosing the investigator rather than vice versa [10]. In spite of this potential pitfall, reporting “selected cases” introduces significant bias and severely limits the validity of such case series. If eligible patients refused to be part of the study or for other reasons did not receive the treatment, it should be noted and the reader should learn about their outcome. If patients were lost to follow-up, it should be documented. The patients who cannot be followed may differ significantly from those who come back. The former may be better, worse, or unchanged compared with the patients reported. If a number of patients are not accounted for, the series becomes a series of “selected cases” [5].

### Natural course of the disease

The implicit comparison for case series is either the natural course of the disease or the course under established treatment. Quite often the authors go to great length to describe a litany of failed treatments in order to describe the treatment-resistant nature of their patients’ conditions which they then go on to cure. However, many, if not most, dermatological diseases have a waxing and waning natural course. The knowledge of what may happen to the patient without the intervention is essential for the reader. For example, many interventions have been shown to halt progression of toxic epidermal necrolysis. This disease-arresting effect was observed usually after several “ineffective” treatment attempts had been tried in the patient. However, in untreated patients the average duration of progression is less than 4 days, which makes the interpretation of treatment that is initiated at or after this point impossible [11].

### Dosages

Information on dosages is an essential part of any treatment regimen. This admonition applies not only to systemic and topical treatment, but also to laser or other surgery. The treatments’ dosage, duration, and titration should be described adequately. For systemic treatments, the amount (total or per kilogram), number of times per day, and duration are important. For topical treatments, the preparation, concentration, vehicle, number of times per day, and duration are important. For laser treatment, “dosage” refers not only to the adjustments and types of laser, but also to the number of sessions that are needed to achieve a certain result. The authors should ideally treat all patients with the same treatment regimen, which may well include a protocol or policy for dose escalation or reduction; for example, steroid tapering. The reader needs to understand what dosages patients received, and if there were any differences among patients, then why some received more or less treatments than others.

### Outcome measures

The outcomes of the therapy should be well defined and clinically relevant. Very often, authors claim clear-cut disappearance of the skin lesions, and this outcome is a well-defined endpoint. However, not all (and in most cases, very few) patients in case series are cured, and the demonstration of clinical improvement is much more challenging. Ideally, the patients are assessed with established outcome measures like the PASI for psoriasis, SCORAD for atopic dermatitis, or CLASI for cutaneous lupus erythematosus. All of these

instruments have inherent and well-recognized limitations, and are not part of normal clinical practice. While desirable, the baseline assessment may be missing for patients treated compassionately. Treating physicians may fear the documentation of these baseline characteristics would constitute clinical research when initially the focus of the treatment is only patient care. In addition, many dermatologic diseases cannot be measured with available scales or instruments and the definition and description of the outcome are challenging.

It is not uncommon for authors to make statements about the therapeutic effect based on percentage improvement. This approach has its pitfalls, particularly if the disease, like most, has more than one dimension (e.g., a combination of pruritus, erythema, and scaling). More often than not, the authors do not describe what constitutes a 50% improvement, and often the content of this improvement remains unclear. The assessment of skin surface involved area is notoriously difficult and inexact. Whereas reference to the surface area involved gives the impression of precision, the accuracy and intra- and inter-observer reliability of these measurements is very low [12].

### Patient perception

The patients’ perceptions of the outcome of treatment should be documented. The patients’ perceptions of treatment are especially important given the difficulties in measuring and reporting outcomes noted above. Many dermatological treatments are tedious and expensive; thus, it is of great importance for clinicians to report whether patients were content with their treatment, and if they were not, what they did not like. If patients discontinue treatment, the reasons should be documented if they are known to the investigators.

### Safety

Safety data derived from small case series are rarely helpful and may be misleading. The data may be misleading if the author implies that the observation that no adverse events were observed in a series is relevant. As a general rule, the estimate of frequency of events derived from case series is imprecise. This imprecision can be estimated even for series without adverse reaction. You can determine the upper 95% confidence interval of the frequency of adverse reactions by referring to available tables, or you can calculate a reasonable approximation of the rate by dividing 3 by the number of patients that were studied [13]. The results illustrate that the small numbers found in case series do not document safety very well. For example, if no adverse events occur in a case series of 10 patients ( $3/10 = 0.30$ ), an underlying adverse event rate of 30% cannot be excluded. No events in 100 ( $3/100 = 0.03$ ) can still mean 3% adverse events. Thus, case series add little to knowledge about safety because they are unlikely to detect rare events and frequently miss common ones.

Usually, large cohort studies, case-control studies, or post-surveillance studies are needed to describe the risks associated with any treatment with authority [14]. Thus, to claim safety based on the absence of adverse effects in series of small sample size is inappropriate. However, the reader should be informed about adverse events or the lack thereof. We think that for case series it is appropriate to give further guidance on expected side effects based on what is known from the literature and previous experience with the treatment.

**Table 12.2** Reasons to be skeptical about case reports and case series.

Lack of test to placebo or vehicle control or standard treatment	Better than placebo or vehicle or just the result of the natural history in a fluctuating condition? Would this treatment perform better than the standard treatment? Case reports and series cannot be used to compare treatments with placebo, vehicle, or standard.
Recruitment bias	Were the patients chosen only based on their likelihood to respond to the treatment?
Information bias	Were the observers not blinded and thus potentially more likely to report favorable outcomes? Third-party assessment may partially overcome this bias.
Survival bias	Were some patients not reported who were originally enrolled? Patients who failed treatment may never have come back, or may have died.
Publication bias	The tendency to publish only positive results. Are there negative case series for the treatment in question?
Confounding	Could there be a systematic influence, beyond the treatment, that may have influenced the outcome? Confounding is hard to assess and cannot be adjusted for in absence of a control group.
Chance	Could the results have occurred by chance? Hypothesis testing is not possible for case series, and thus it is not possible to assess whether the result may reflect chance. While the population response rate or the overall natural course of the disease is helpful, it may not reflect the particular selected cases. Ideally, the reporter would not publish two or three dramatic cures but use these successes as a starting point for further observations, which would not include these first ones.
Regression to the mean	Were the patients recruited during a particularly bad phase of a fluctuating disease which would in most cases improve over time? Such effects are well documented in placebo-controlled studies.
Lack of formalized quality control	Is there any external formalized quality control to exclude fraud or data manipulation? Is there any conflict of interest?
Retrospective collection	Was the study only a retrospective collection of cases? Did the authors make sure that all patients in the institution that fit the inclusion criteria were included?

## Conclusions

Case series are, for pure reason of quantity, important sources of information about dermatological therapies, which is rather unfortunate, but unlikely to change in the near future. Owing to the lack of control groups, they can demonstrate efficacy of treatment only under rare circumstances (e.g., when the effect is dramatic and no other effective therapy is available). Given their low level of evidence and the many reasons to be skeptical about their findings (Table 12.2), it is mandatory that they are very well reported. Owing to their widespread use in the literature, there have been multiple attempts to classify and rate their quality; the referenced source is the most comprehensive [15].

If well designed, executed and reported, case series can be important clinical evidence that allows us to learn about alternative treatments before and perhaps in the absence of controlled trials. A poorly reported case series is likely to be unconvincing at best and misleading at worst, and thus it is important to stress that controlled high-quality clinical trials should be conducted if feasible.

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# What makes a good prevalence survey?

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## Introduction

In addition to providing an estimate of the burden of skin disease in a given community, prevalence surveys (also known as cross-sectional studies or just “surveys”) make it possible to estimate the potential demand for medical facilities and the economic impact of a disorder. Comparison of data from prevalence surveys conducted in different populations with varying dietary and lifestyle habits may allow tentative inferences to be drawn about the association between a certain disease and its possible triggering factors [1]. Sometimes, sequential surveys are used to provide some evidence of effectiveness of an intervention. Prevalence surveys thus offer a means of estimating the prevalence of disease, its impact, and possible associations with risk factors, including population-based interventions. It is important to draw inferences only from high-quality surveys. But how do you tell a good prevalence survey from a bad one? This chapter discusses criteria that can be used to assess the quality and relevance of cross-sectional studies, with an emphasis on estimation of disease prevalence.

## The importance of clear reporting

Prevalence surveys, like other study designs, are prone to poor reporting and to bias, which results in reduced quality. Reporting refers to the extent to which items that should be described in a prevalence study are included in the study report. Study quality, on the other hand, is a judgment of how well the study was designed and executed in terms of reduction of risk of bias. Making a distinction between poor reporting and poor study quality is important as four scenarios are possible: a poor study that is well or poorly reported, and a good study that is well or badly reported [2]. Only well-reported studies make it possible for the reader to come to a judgment whether the study was of good quality or otherwise. In other words, complete reporting is a prerequisite to enable risk of bias (quality) to be judged. Thankfully, clear guidance on the reporting of observational studies have been developed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) group [3]. Although many of the recommended reporting items in STROBE are common to cohort, case-control, and cross-sectional studies, a specific checklist of 25 items for cross-sectional studies has been developed (<http://www.strobe>

-statement.org/fileadmin/Strobe/uploads/checklists/STROBE\_checklist\_v4\_cross-sectional.pdf).

Quality of reporting of observational studies in dermatology has been mixed, as was illustrated for prevalence studies of psoriasis in the second edition of this textbook [4]. One systematic review of 138 observational studies in dermatology assessed by the European Dermato-Epidemiology Network found that some key areas, such as sample size calculations, missing data, losses to follow-up, statistical methods, and funding sources, were frequently unreported [5]. The findings were broadly similar for the main types of observational studies, including cross-sectional studies. The conclusion is a simple one: observational studies in dermatology must report the key items that are needed by readers. Thankfully, many dermatology journals now make it a requirement for all observational studies to adhere to the STROBE reporting checklist [6], although how well journal reports stick to such guidance is worthy of further research.

## Quality criteria

A comprehensive guideline for evaluating the *quality* of prevalence surveys was that published in 1998 by Loney *et al.* [7]. They proposed eight main quality criteria, of which we suggest that the seven shown in Box 13.1 are useful for determining the quality of a dermatological prevalence survey. Each item is discussed in more detail.

### Specification of the target population

Published prevalence surveys should give a definition of the target population, which is the population to whom the researchers wish to generalize their results. Information about the geographical area covered, as well as age and gender, should be included. Whether certain population subgroups are excluded (e.g., certain ethnic groups) should be mentioned.

### Employment of adequate sampling methods

In most cases, it is impossible to survey the whole population of interest. It is therefore necessary to draw a sample that is representative of the population of interest. The best sampling technique is random sampling, in which a group of people are selected at



**Box 13.1** Criteria to consider when assessing the quality of prevalence surveys in dermatology

**Seven criteria that should always be assessed:**

- Was the target population specified?
- Which sampling method was employed? Is the survey based on a random sample or a whole population?
- Was the sample size adequate?
- Was the response rate adequate?
- Was information given on nonresponders?
- Was a valid and repeatable disease definition given?
- Have reasonable efforts been made to reduce observer bias?

**Other factors worth looking for:**

- Were inclusion criteria specified?
- Was information on persons actually studied reported in detail?
- Were known and validated instruments used for measurement of the health outcome?
- Were the terms “incidence” and “prevalence” correctly applied?
- Were confidence intervals or standard errors presented for the estimates of prevalence?

Adapted from Loney *et al.* 1998 [7].

random for study from a larger group (population). Each person is chosen entirely by chance, thereby reducing the likelihood of a selection bias favoring one group of people over another.

Cluster sampling – that is, sampling clusters of people, such as a random sample of villages within a region – is acceptable provided that the methods are clearly described and that the precision of the final prevalence estimate incorporates the clustering effect. Convenience samples – for example, a street survey or interviewing lots of people at a public gathering – do not provide a representative sample of the base population.

### Adequate sample size

The larger the sample, the narrower will be the confidence interval around the prevalence estimate, making the results more precise [1]. As no observed sample value exactly equals the population value, the confidence interval is a necessary parameter that describes the range of plausible values for the population parameter. Often, a “95% confidence interval” is quoted. The figure of 95% reflects the strength of belief that the computed interval actually contains the unknown parameter value [8].

The sample size required to estimate the prevalence of a disease with a certain degree of precision can be calculated. For example, following a review of surveys concerning the prevalence of psoriasis presented in the last edition of this textbook [4], we calculated that if the prevalence of psoriasis is assumed to be 2%, a sample size of 753 would be needed in order to obtain an error rate of  $\pm 1\%$  at the 95% confidence level. So with this sample size, and a real psoriasis prevalence of 2%, the prevalence value resulting from a survey could vary between 1% and 3%. The accepted error rate could vary depending on the assumed absolute prevalence of a disease. If a disease has a prevalence of around 10%, an error rate of 2% could be acceptable, resulting in a prevalence estimate with 95% confidence intervals varying between 8% and 12%. As the prevalence of psoriasis is not assumed to be that high, though, an error rate higher than 1% could result in imprecise outcomes. In order to guarantee the defined confidence level and error rate, and therefore ensure a specified degree of precision, it is necessary to define the

actual final sample size by subtracting the nonresponders from the initially determined sample size.

### Adequate response rate

If only a proportion of the invited people participate in a survey, selection bias may occur, thus affecting the validity of the findings [9]. Individuals affected by a certain disease could either respond more often than healthy people or rather tend towards nonparticipation. For population surveys, a response rate of 66–75% has been recommended as generalizable in the literature [10].

### Information on nonresponders

It is necessary to obtain information about nonresponders in order to make sure that they do not systematically differ from survey responders in terms of factors such as sociodemographic characteristics or the presence of disease. Researchers should try to follow up individuals who do not consent to participate in a survey and ascertain their reasons for nonresponse.

### Valid and repeatable disease definition

An important quality criterion for prevalence surveys is the presence of a standardized definition of the disease under investigation. A good disease definition is valid and repeatable. The term “validity” refers to the sensitivity (discerning as many cases of disease as possible) and specificity (excluding as many noncases as possible) of the definition [11]. A disease definition’s validity has to be tested on an independent sample before it can be used on the study population.

Ideally, a repeatable disease definition leads to similar results between several observers or within replicate measurements taken by the same observer. Testing of this criterion is also necessary before adopting a disease definition.

In the field of dermatology, valid and repeatable disease definitions are rarely to be found in prevalence surveys. Not one of the 22 surveys of psoriasis prevalence assessed in the last edition of this book assessed contained a valid disease definition – a pattern that has continued in subsequent studies [12,13], reflecting a research need to develop valid and reliable diagnostic criteria for psoriasis in population surveys.

### Reduction of observer bias

Observer bias may occur when a prevalence survey is based on clinical examination or on interviews. If there are several observers, their assessment concerning the presence or absence of a disease or of its severity could vary considerably. Even if only one examiner is responsible for the whole survey, observer bias may occur – for example, if the examiner has a lower threshold for diagnosing borderline cases of psoriasis in comparison with others or if they have a personal interest in a certain outcome, such as a company with a new psoriasis product that wishes to show that psoriasis is a big problem.

Thus, an attempt to minimize observer bias is mandatory for every prevalence survey. This task may be accomplished by adequate training of the examiners and by teaching them to rate the presence or absence of a disorder in the same standardized way. A comparison of the results of all observers may also show whether there is any inter-observer variability. If there is only one observer, it should be made clear before the onset of the survey that they have no personal interest in a particular outcome. Other methods of reducing observer bias include the use of photographs, which can then be assessed by an independent panel.



## Additional criteria

Other factors that should be taken into account when a prevalence survey is planned include the following.

### Specification of inclusion criteria for the study population

To allow for comparability between different prevalence surveys, it is important to specify inclusion criteria. These should comprise information about the age range and, if appropriate, gender and ethnic group of the individuals to be studied.

### Information on studied individuals

In addition to specifying inclusion criteria to denote who is eligible for study, a good prevalence survey should give basic demographic information about the individuals actually studied. Given that non-response is common, data on the population that is actually studied might differ from the specified inclusion criteria. For example, if a survey of psoriasis sets out to include all adults between 20 and 80 years of age, but individuals older than 75 years do not participate, the age range of the actually persons studied runs from 20 to 75 years. Valuable information about the individuals studied comprises at least the age range, ethnic group, and sex distribution.

### Measurement with valid instruments

A good prevalence survey describes the examination methods which led to its results. Furthermore, the instruments employed should be valid, displaying a high sensitivity and specificity. If an agreed standard measurement of a disease exists, with tested validity and reliability, then it should be employed, otherwise any other instruments used should have been tested previously in relation to the standard instrument.

In prevalence surveys, one method of measurement is clinical examination of the study population, especially when dealing with surveys of visible dermatological diseases. If this examination is performed by one or more trained specialists, a valid measurement is often assumed, since specialists are often used as a reference standard where no objective tests are available, as in psoriasis. Other common methods are questionnaires and interviews. Ideally, the questionnaires employed should have been tested for validity before being used on the study population [14].

### Correct application of epidemiological terms

It cannot be assumed that published prevalence surveys always apply the correct epidemiological terms for their findings. Sometimes, the terms “prevalence” and “incidence” are misused, the one being applied when in fact the other has been determined. A careful evaluation of the results with regard to their correct epidemiological relevance is therefore necessary.

In our previous review of prevalence surveys of psoriasis, one out of 22 surveys applied the term “incidence” (number of new cases per unit time) to its findings [4], when in fact the prevalence (number of cases existing at one point in time) had been determined.

### Confidence intervals or standard errors

The results for the prevalence of a disease derived from a prevalence survey provide only an estimate of the true prevalence in the larger population. Confidence intervals provide a range that contains the true population prevalence estimate with a certain degree of assurance, thus indicating the level of confidence one can have in the estimates. The degree of assurance commonly used is 95%.

Confidence intervals are influenced by the sample size. The larger the sample, the narrower the confidence interval and the more precise the estimate [15]. By calculating and mentioning confidence intervals for their prevalence estimates, quality prevalence surveys indicate their precision.

The standard error as a measure of the amount of sampling variability is also influenced by the sampling size [15]. The standard error reflects how much the estimate for prevalence fluctuates from sample to sample. A small standard error shows that different samples do not greatly affect the estimate for prevalence derived from the survey.

Thus, both confidence intervals and standard error are important for describing the reliability of the outcome of prevalence surveys. One of them should be computed and always reported in the results of a prevalence survey.

## Other checklists and scales

Searching for quality assessment tools is not straightforward as, unlike the EQUATOR Network – the resource center for good reporting of health research studies (<http://www.equator-network.org/>) – we are unable to find any resource that specifically collates instruments that assess study quality. We have searched the EQUATOR website and PubMed using terms “risk of bias AND assessment AND tool AND (surveys OR cross sectional OR prevalence)” and variations on these terms in order to identify further developments in this field.

Sanderson *et al.* [16] undertook a systematic review of tools used to assess the quality and susceptibility to bias for observational studies in epidemiology in 2007 which included checklists and scales that were recommended for a variety of study designs, including cohort, case-control, and cross-sectional (prevalence) studies. Only half of the tools assessed provided details on how they were developed. Most tools included items that related to methods for selecting populations (92%), how the study variable were measured (86%), sources of bias that were specific to the study design (86%), how confounding was considered (78%), and appropriateness of statistics (78%). The weighting and distribution of domains across the various scales was quite variable. The systematic review identified 19 instruments that could be applied for cross-sectional studies, six of which had been designed exclusively for cross-sectional studies [17–22]. Two of these were simple checklists [17,18], one was a checklist with additional judgments included [19], and three were scales [20–22]. None of the scales considered conflict of interest, and no recommendations were made by the reviewers on which instrument is “best” for cross-sectional studies. The authors instead commented on the lack of empirical evidence on which factors should be included in order to assess quality of observational studies, and that any new instruments should use evidence-based principles in their development and reporting.

A subsequent broader systematic review by Shamliyan *et al.* [23] assessing the quality of observational studies that examine incidence or prevalence and risk factors for diseases identified 46 scales and 51 checklists, only five of which were created for prevalence studies [23]. They commented that most numerical scales along with their arbitrary weightings of items were meaningless. They also concluded that poor quality of reporting was not separated sufficiently from poor study quality, and that it was rare for such scales to distinguish between internal and external validity.

The quality methods guide developed by the US Agency for Healthcare Research for Comparative Effectiveness Reviews in

2012 indicate some design-specific criteria to look out for in cross-sectional studies that are sometimes used to assess benefits of interventions [24]. These included uniform application of inclusion/exclusion criteria to all groups, adequate control for confounding, performance, detection, attrition bias, and publication bias.

The systematic review by Shamliyan *et al.* prompted Hoy *et al.* [8] to develop one of the most promising scales by Leboeuf-Yde and Lauritsen [25] that had been used to assess the prevalence of back pain in Nordic countries. Using rigorous methods to enhance inter-observer agreement, they suggested a checklist of four items for assessing external validity and seven items for internal validity, as summarized in Box 13.2. Responses for each item are classified as either low risk of bias or high (which includes unclear). Hoy *et al.* tested inter-rater agreement for the 11 items and found excellent levels of agreement for the individual items of the tool and moderate agreement for the summary risk of bias assessment. Further practical details on how to use this tool are given in the appendix of the online version of this report at <http://www.sciencedirect.com/science/article/pii/S0895435612000790>. Interestingly, all of the items mentioned in the checklist we developed in Box 13.1 are mentioned in the Hoy *et al.* checklist with the exception of items 8–11 inclusive. The division into items that denote internal from external validity in the Hoy *et al.* checklist and the fact that good inter-observer agreement has been shown for most of its items may make it an attractive checklist for use in assessing the quality of future prevalence surveys.

## Conclusion

Cross-sectional prevalence surveys are useful for estimating disease burden and costs, and they are sometimes very straightforward to undertake. As in any other study, it is possible to do a good or bad quality prevalence survey, and the factors outlined in Box 13.1 or 13.2 should be heeded when designing and setting up a prevalence survey. A good study design and execution does not always mean

that those reporting the results have included the important features. Better reporting of the quality factors outlined in this chapter is therefore crucial in order to allow readers to decide whether the results of a prevalence survey are valid and relevant to their population.

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**Box 13.2** Checklist of four external validity and seven internal validity items to look out for when evaluating the quality of a cross-sectional (prevalence) study that has shown good inter-observer agreement

### External validity

- 1 Was the study's target population a close representation of the national population in relation to relevant variables?
- 2 Was the sampling frame a true or close representation of the target population?
- 3 Was some form of random selection used to select the sample, OR was a census undertaken?
- 4 Was the likelihood of nonresponse bias minimal?

### Internal validity

- 5 Were data collected directly from the subjects (as opposed to a proxy)?
- 6 Was an acceptable case definition used in the study?
- 7 Was the study instrument that measured the parameter of interest shown to have validity and reliability?
- 8 Was the same mode of data collection used for all subjects?
- 9 Was the length of the shortest prevalence period for the parameter of interest appropriate?
- 10 Were the numerator(s) and denominator(s) for the parameter of interest appropriate?
- 11 Summary item on the overall risk of study bias.

Source: Hoy *et al.* [8]. Reproduced with permission of Elsevier.

# Critical appraisal of pharmacoeconomic studies

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## Introduction

Dermatologists are increasingly interested in pharmacoeconomic studies, with the realization that funds for health care are limited. This chapter outlines the four fundamental types of pharmacoeconomic studies (Table 14.1), gives dermatological examples, and concludes with a discussion of the necessary items for such studies. Readers can then critically appraise these studies.

## Cost analysis

Cost analyses are the most fundamental pharmacoeconomic study; they deal solely in costs of therapeutic interventions. Researchers can derive costs from either micro- or macro-costing. Microcosting involves enumerating each component of a therapeutic strategy and then determining the cost of each component.

Langan *et al.* [1] determined the annual cost of providing narrow-band ultraviolet B (nbUVB) phototherapy for psoriasis from a hospital perspective. Using the microcosting approach, they enumerated operational costs, nursing costs, consultant time, secretarial time, physics support, and nonconsultant hospital doctor costs. The total annual amount was €53 555 from the hospital perspective and €325 from the individual patient perspective. They found that 70% of the total annual cost of nbUVB phototherapy was due to personnel staffing. The remaining 30% of the total cost could be attributed to overhead costs for the phototherapy department. Although the cost of nbUVB for psoriasis is significant, they concluded that it incurs less cost compared with hospitalization and inpatient treatment. This study was conducted in Ireland, thus reflecting the inpatient perspective; in the USA, psoriasis patients are rarely treated in the inpatient setting.

Bialy *et al.* [2] compared the cost of Mohs micrographic surgery and traditional surgical excision (TSE) performed by otolaryngologists for the treatment of facial and auricular nonmelanoma skin cancer (NMSC). They itemized costs of the surgery, pathologic analysis, reconstruction, facility fees, and follow-up visits. They concluded that Mohs is cost comparable to two sequential TSEs with permanent section in the office (\$937 vs \$944) and was statistically significantly less costly compared with facility-based TSE with frozen section (\$956 vs \$1399). In another study, Rogers Coldiron [3] also compared the costs of treatment of NMSC, specifically

basal cell carcinoma (BCC) on the central cheek and squamous cell carcinoma (SCC) on the forearm. They performed a cost analysis of the following treatment modalities: electrodesiccation and curettage (EDC), imiquimod immunotherapy, Mohs micrographic surgery, TSE with permanent section margin evaluation in an outpatient setting, surgical excision with frozen section in both an outpatient and inpatient setting, and radiation therapy. They found that EDC is the least expensive option for treating an NMSC (\$471 BCC cheek and \$392 SCC arm). Similar to the analysis by Bialy *et al.* [2], they found that other lower cost treatment options for NMSC include office-based procedures such as Mohs micrographic surgery or TSE, or imiquimod therapy.

Macrocosting determines the overall cost to care for a particular disease, usually with a population-based approach. Kirsner *et al.* [4] evaluated the cost of hospitalization for dermatology-specific and diagnosis-related groups (DRGs) using the Medicare Provider Analysis and Review 1990–1996 database, which contains information for all Medicare beneficiaries using hospital inpatient services. The authors used codes for various dermatologic conditions and found that, in 1996, Medicare reimbursement was US\$52 million for dermatology-specific DRGs and US\$840 million for dermatology-related DRGs, a combined total of US\$892 million.

Cost analyses are useful as sources of rigorous cost accounting and as the basis for other pharmacoeconomic studies. However, they do not account for outcomes and potential side effects. Without accounting for the outcomes, the value of the therapeutic intervention cannot be easily measured. A costly medication that does not work well and does not provide quality outcomes has very little value. On the other hand, a costly medication that routinely improves lives may have very high value.

## Cost-effectiveness analysis

Cost-effectiveness analyses (CEAs) are one form of pharmacoeconomic analyses that incorporate both costs and outcome. The results of CEAs are presented as a cost-effectiveness ratio (CE ratio), with costs in the numerator and health outcomes in the denominator. The ratio is a measure of value; the smaller the ratio, the fewer the resources required for a given unit of health outcome. Costs are determined in the same manner as for cost analyses, as discussed

**Table 14.1** Summary of the advantages and disadvantages of different types of pharmacoeconomic analyses.

Type of pharmacoeconomic analysis	Advantages	Disadvantages
Cost analysis	Sources of rigorous cost accounting  Basis of other pharmacoeconomic studies	Does not account for outcomes and side effects  Does not measure the value of the therapy
Cost-effectiveness analysis	Accounts for outcomes and side effects  Measures value of the therapy	Outcomes are not standardized across disease processes  Results are not weighted according to importance
Cost-utility analysis <sup>a</sup>	Accounts for outcomes and measures value of therapy  Results are standardized	Need to invoke some external criterion of value to interpret results
Cost-benefit analysis	Accounts for outcomes and measures value of therapy  Does not need external criterion of value to interpret results	Assigning monetary value to health may be offensive  May be difficult to measure benefits in monetary terms for expensive and complex therapies

<sup>a</sup>Often called cost-effectiveness analysis.

above. The health outcomes are generally measured by some biological unit, such as intra-ocular pressure for glaucoma interventions, or by life-years saved for cancer chemotherapy.

CEAs compare at least two therapies – usually a new therapy is compared with a currently available therapy. A CEA that compares two therapies is called an incremental CEA; the additional costs that one therapy would entail are compared with the additional benefits that it provides. This CEA is in contrast to an average CEA in which the therapy in question is not compared with anything. However, the average CEA approach does not provide useful information to the policymaker or the clinician unless the currently available therapy is to do nothing.

Bergstrom *et al.* [5] published a CEA comparing the foam form and cream and solution combination form of topical clobetasol propionate for the treatment of psoriasis. They used the psoriasis area and severity index (PASI) score to measure their outcome. The difference in cost per change of one PASI unit using foam vs. cream and solution (US\$21.60 vs \$16.42 per PASI unit, respectively) was \$4.18; this was not found to be statistically significant ( $P = 0.20$ ).

CEAs provide information about the value of the therapeutic intervention in question by accounting for the outcomes of the therapy. However, the outcome measure is not standardized and therefore cannot be used to make comparisons with other disease processes. For example, a reasonable outcome measure for a new therapy for seborrheic dermatitis may be dollars per clear scalp. However, this measure cannot be used to compare with the CE ratio of new therapies for disparate diseases such as onychomycosis, venous ulcers, or acne. Even if “clear skin” is used as the outcome measure, it cannot be used to make comparisons with nondermatological problems. Another problem with CEA is that the outcomes are not weighted according to their importance. For instance, assume that new therapies for scalp psoriasis, onychomycosis and venous ulcers were cost effective compared with their respective

current therapies. Policymakers may not be able to incorporate all the therapies into their formulary because of budgetary constraints. They would need to decide which is the most important outcome: clear scalp, smooth nails, or a healed ulcer. A better situation would be to have the outcomes standardized and weighted according to value so that policymakers could compare CEA results across disease processes.

### Cost-utility analysis

Cost-utility analyses (CUAs) provide outcomes that are standardized and weighted. CUAs give rise to a ratio similar to that of a CEA except that the outcomes are measured in quality-adjusted life-years (QALYs). Note that many health services researchers use the two terms CUA and CEA synonymously [6]. QALYs reflect both the additional quantity of life that a therapy extends and also the quality of that additional amount of life. The latter measurement is particularly important in dermatology, where therapeutic interventions rarely save lives but often improve quality of life. In the QALY approach, quality of life (QoL) is measured by a set of weights called utilities, one for each possible health state, that reflect the relative desirability of the health state. The reader is encouraged to consult other references for detailed explanations of utilities [6,7]. By incorporating QoL and by standardizing the outcome measure with QALYs, a dermatology CUA such as acne therapy can be compared with a mortality-impacting CUA such as breast cancer therapy. There are few published dermatological CUAs, but a recent paper providing dermatologic utilities will provide a strong foundation for future CUAs [8].

Freedberg *et al.* [9] published a CUA comparing a one-time screening strategy for melanoma with a no-screening strategy. They primarily used life-years saved as their outcome measure, but they also used an estimate of utilities to estimate a QALY outcome. They found the CE ratio for the screening program to be US\$29 170 per life-year saved and US\$30 360 per QALY. While the strategy of screening once in a lifetime may not mimic reality, the analysis was a good beginning for investigating the cost effectiveness of melanoma screening. Before interpreting the QALY result (US\$30 360 per QALY), readers should realize that the criterion for cost effectiveness, called the CE threshold, is arbitrary and open to debate. A cost-effective therapy is one that delivers more QALYs per dollar (or costs fewer dollars per QALY) compared with some benchmark. Researchers consider therapies less than US\$50 000 per QALY to be relatively cost effective, whereas those greater than US\$175 000 per QALY are not [10–12].

Losina *et al.* [13] published a CUA comparing four different screening strategies for melanoma: background screens every 5 years, one time, every 2 years, and annual screening. The screening populations were the general population, having one first-degree sibling with melanoma, and two first-degree relatives/siblings with melanoma who were defined as being at highest risk. Inputs to their model were from the literature. Outcome measures included years of life saved and QALYs. They found that the most cost-effective strategy was a one-time screening of the general population at the age of 50 (\$10 100/QALY gained) and screening every 2 years in siblings of patients with melanoma (\$35 500/QALY for first-degree relatives and \$14 700 for highest risk siblings). These CE ratios were consistent with CE ratios for the recommended screening of other types of malignancies, such as breast and colorectal cancer.

With the advent and rising popularity of teledermatology, Parsi *et al.* [14] published a CEA comparing conventional in-office care



with a patient-centered online model for follow-up treatment of patients with psoriasis from the societal perspective. They did not find a statistically significant difference in mean change in QoL outcome, measured by dermatology life quality index (DLQI) scores, between the two groups. The DLQI score was converted to the EQ-5D (European Quality of Life Instrument-5 Dimensions) utility score using a formula. There was also no statistically significant difference in mean improvement in quality-adjusted life expectancy between the groups. However, the cost of follow-up psoriasis care through the online model was 1.7 times less than the cost of in-person visits. The paper reported both average and incremental CE ratios; the incremental CE ratio was \$16318 per QALY saved by the in-office group over the online group. This study concluded that costs were saved with online-care follow-up models while maintaining standard effectiveness of care similar to an in-office visit; however, their conclusions seemed based upon the average CE ratios rather than their incremental CE ratio.

Blank *et al.* [15] compared oral alitretinoin with supportive care plus emollients for the treatment of severe chronic hand eczema (CHE) nonresponsive to standard therapy (topical corticosteroids). Health states represented were clear/almost clear, mild/moderate, and severe nonresponders. Inputs were derived from two clinical trials. Direct costs were derived from market prices for drugs and insurance data for indirect costs. Clinical effectiveness was reported in QALYs extrapolated from data from severe psoriasis. They assumed that CHE patients had the same QoL impact as psoriasis patients and utilized the DLQI score reflecting the psoriasis severity. The DLQI score was then converted into EQ-5D utility weights using the same mapping formula in the above study. They concluded that treatment with alitretinoin resulted in a direct cost of €2212 and an average gain of 0.230 QALYs. Incremental CE ratio of using oral alitretinoin was determined to be €14816/QALY gained.

Of note, the EQ-5D measures health status very generally. Respondents describe the burden of their condition (no, moderate, and severe problems) in reference to five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [16]. Preliminary data are conflicted as to whether the EQ-5D adequately estimates utilities [17]. While the DLQI is a validated instrument measuring disability and may convert well to the EQ-5D score, it remains to be seen whether the EQ-5D can estimate utilities well enough for CEA [16].

## Cost-benefit analysis

Cost-benefit analyses (CBAs) differ from CEAs and CUAs in that the results are reported as differences between the costs and health benefits of the therapeutic program. The health benefits are represented in monetary terms, usually by asking subjects how much they would be willing to pay for the therapy. The interpretation of a CBA is also different from that of a CEA or CUA. The CEA/CUA results give the value of a particular therapy relative to a standard therapy. However, in order to decide whether the new therapy is worth adapting at the expense of forgoing a different therapy, readers must invoke some external criterion of value, such as the CE threshold. The CBA, in contrast, allows the investigator to determine whether the therapy is worth the costs without an external criterion since all benefits in CBA are valued in monetary terms.

We [18] compared Goeckerman therapy with methotrexate for psoriasis using CBA in addition to the CUA described above. We queried a sample of “society” for the amount that they would be

willing to pay for each therapy if their insurance company did not provide for it. We found that there was no net benefit of Goeckerman over methotrexate. When we compared each therapy with a “do nothing” approach for different severity levels of psoriasis, only methotrexate produced net benefits for severe psoriasis.

Detractors of CBA cite a wariness of assigning monetary value to health because of moral and ethical issues [7]. However, proponents of the method point out that decision-makers who use the CEA/CUA implicitly place a monetary value on the health outcome since they choose some threshold below which they consider that the outcome is worth the cost [6]. Another disadvantage to the CBA method lies in the validity of the “willingness to pay” estimate of the value of the health benefits. Fortunately, many dermatological interventions are neither overly expensive nor complex, and thus it is reasonable to expect subjects to be able to conceptualize how much they would be willing to pay for a dermatological therapy.

## Guidelines for critical appraisal of pharmacoeconomic studies

Box 14.1 presents a checklist for readers of pharmacoeconomic analyses.

### Framework

To evaluate any pharmacoeconomic analysis, readers must bear in mind several points about the framework of the study. First, the study needs to be clear about the perspective of the analysis. Three main perspectives of a pharmacoeconomic analysis include the individual patient, the third-party payer, and society. The perspective dictates the cost used in the analysis (see below). The Panel on Cost-effectiveness in Health and Medicine has recommended including an analysis from the societal perspective [19]. Second, the target population to which the intervention is directed should be explicitly stated. Third, all pharmacoeconomic studies should be

#### Box 14.1 Checklist for readers of pharmacoeconomic analyses

##### Framework

- Perspective of analysis
- Target population for intervention
- Description of comparator programs

##### Data and methods

- Diagram of pathway of health intervention
- Type of outcome used
- Methods for obtaining cost, effectiveness and QoL
- Costs are market rates and not charges
- Critique of data quality
- Assumptions for input data are tested with sensitivity analysis
- Inflation and discount rates noted

##### Results

- Societal perspective (reference case)
- Sensitivity analysis

##### Discussion

- Summary of reference case
- Implications of sensitivity analysis
- Limitations
- Relevance to health policy decisions

Source: Siegel *et al.* [19].

incremental analyses, comparing at least two therapies unless no standard of care exists. Pure cost analyses can be an exception to this guideline since they can be used purely to account for cost. As noted in the Parsi *et al.* [14] study of teledermatology, different conclusions can be made if one uses average versus incremental analyses.

## Data and methods

Pharmacoeconomic studies should detail the pathway of the health intervention being analyzed, preferably with diagrams. In this way, readers can determine whether the proposed flow of health care is comparable to their own. If not, then the analysis may not be relevant. The study should be explicit in the types of outcomes used in the analysis, whether it is QALYs, life-years saved, or a disease-specific outcome. Awareness of outcome measures is especially important in analyses utilizing non-disease-specific health measures such as the EQ-5D. The methods for obtaining cost, effectiveness, and QoL measures should also be clear. If primary data are not available, the assumptions for using secondary data must be clearly stated, such as the alitretinoin study using psoriasis utilities as a proxy for CHE utilities, and a sensitivity analysis performed to ensure that the results are robust to these assumptions. A critique of the quality of the input data should also be explicit.

Several points about cost should be mentioned. The perspective of the study influences the costs used in the analysis. If an analysis is performed from the perspective of the individual patient, then only the costs relevant to the patient should be considered. These costs would include the copay that is involved with the physician visit and the drug, and the time off from work that is needed to see the doctor. Assuming that the drug is covered by insurance, the actual cost of the drug would not be factored since it is irrelevant from the perspective of the patient. On the other hand, third-party payers would be concerned about the cost of the drug as well as the cost of the physician, but not the copay or the time off from work. The analysis performed from the societal perspective would factor in costs that affect all members of society: the cost of the drug, the physician, and the time off from work, as well as any impact on family members. In the Blank *et al.* [15] study for CHE, the market prices of the drugs were used because the perspective was from the Swiss health system.

It is also useful to consider the categories of cost when evaluating a pharmacoeconomic analysis. Direct healthcare costs are the cost of the resources that directly provide the therapy. These include physicians, medications, laboratory monitoring, and radiography, for example. Indirect costs are those resources that relate to time and productivity. Indirect costs include the cost of the consumption of the time that the patient took from work, volunteer time, and family-leisure time. It can also include costs associated with the loss of or impaired ability to work secondary to illness.

The theoretically correct manner to estimate cost is by determining the opportunity cost. Opportunity costs consist of the value of forgone benefits; some other program must have been forsaken in order to pay for a particular therapeutic regimen. For instance, in a developing country, it might be necessary to sacrifice an education program in order to implement a vaccination program. However, sometimes one cannot assume perfect competition between two programs, so health-care prices may not approximate true opportunity costs. Instead, health economists use existing market prices to estimate costs. Readers should be wary of analyses that use charges to estimate costs, since charges rarely approximate the market prices of services. In general, analyses performed from the

societal perspective approximate the cost of physician and hospital services by using the Medicare reimbursement rate and estimate the cost of medication using the average wholesale price.

If the study analyzes the therapy over a long time course, then there needs to be an explanation of methods to account for inflation. Also, because, in general, people prefer to have money and benefits now rather than in the future, future costs and benefits in the analysis must be discounted. Experts recommend using a 3% discount rate [19].

## Results and discussion

Results should, at the minimum, be reported from the societal perspective. Results of sensitivity analysis should also be discussed. When assumptions have been made for the input data, those variables should be varied within reasonable clinical parameters. If the results change with variations in those variables, then readers should be wary of the robustness of the results. Finally, the relevance and limitations of the results to health policy issues need to be discussed.

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# Comparative effectiveness research: what it is and how to assess its quality

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## Why do comparative effectiveness research?

In spite of ongoing medical advances and cutting-edge biomedical research worldwide, much of medical decision-making by health-care providers and patients, especially in the field of dermatology, remains based on little scientific evidence. Randomized controlled trials (RCTs) have long been considered the gold standard of medical intervention studies. However, there is increasing recognition that the “average” effect that is measured in RCTs does not necessarily apply to all participants within a trial, nor is it reflective of how an intervention performs in the “real world” [1].

Whereas one of the great strengths of an RCT is its strong internal validity (i.e., similarity of characteristics in the control and intervention groups, resulting in high likelihood that the results of the study are “true”), RCTs generally have poor external validity (i.e., are not generalizable to a larger patient group). Characteristics of RCTs that contribute to poor generalizability include relatively short study periods (typically on the scale of weeks to months), specialized study populations with strict inclusion and exclusion criteria, comparison with placebo as opposed to a clinically relevant active comparator, and measurement of outcomes that may not be important to patients or relevant to clinical practice.

Results from RCTs, therefore, measure efficacy or how an intervention performs in an ideal, carefully controlled setting rather than the real-world clinical setting. The potential effects of strict inclusion and exclusion criteria of RCTs are exemplified by a study of a Spanish registry of psoriasis patients receiving biologic or oral systemic treatment which found 30% of patients to be ineligible for and unrepresented in RCTs [2]. This omission has important clinical consequences, as the patients who were ineligible for RCTs were found to be at higher risk of developing serious adverse effects compared with those who would have been eligible. This finding highlights the importance of determining not only which interventions are safer and perform the best, but also in which subpopulations of patients safety and performance are maximized.

In order for health care providers and patients to make informed medical decisions, they require guidance from studies that measure effectiveness (i.e., how an intervention performs in the clinical setting). Comparative effectiveness research (CER) is one method by which different medical interventions can be compared with one

another in order to determine the most effective methods of prevention, diagnosis, treatment, or monitoring for a particular medical condition.

CER is not a new concept, as comparative studies have been performed for many years. However, an interest in CER has been renewed due to the recognition of a need to address the aforementioned knowledge gaps in health care. In response, there have been international efforts to increase and incorporate CER into clinical practice. In the UK, the National Institute for Health and Clinical Excellence utilizes the synthesis of existing research and economic modeling to guide evidence-based medical decisions for the purposes of reducing variations in clinical practice, creating management guidelines, and setting quality standards. In Australia and Canada, CER efforts have been focused on pharmaceutical interventions and managed by the nationally run Pharmaceutical Benefits Advisory Committee and Common Drugs Review, respectively.

CER efforts in the USA have been slower to develop and were stimulated by the US Congress's establishment of the American Recovery and Reinvestment Act (ARRA) of 2009 which allocated \$1.1 billion to support CER practices. Under this law, the Institute of Medicine (IOM) was also charged with the task of establishing a priority list of CER topics with stakeholder (e.g., health-care professional, patient, policy maker) input to help focus national CER efforts. Of particular relevance to the field of dermatology, psoriasis, chronic lower extremity wounds, and acne are included among the top 100 identified priority topics for CER [3]. To further promote and fund research to guide medical decision-making, the Patient-Centered Outcomes Research Institute (PCORI) was created by the 2010 Patient Protection and Affordable Care Act. PCORI also includes an independent, federally appointed methodology committee whose purpose is to develop methodologic standards for patient-centered outcomes research ([www.pcori.org](http://www.pcori.org)) [4].

## What is comparative effectiveness research?

The IOM National Priorities Committee defines CER as follows:

Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods

to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels [3].

Several other definitions of CER exist, all of which encompass the basic characteristics of CER and have been summarized by the IOM [3]. An essential defining concept of CER that differentiates it from other studies, namely RCTs, is that of effectiveness as opposed to efficacy. The differences between efficacy and effectiveness research are described in Table 15.1.

## Methods in comparative effectiveness research

CER, as it has been recently defined, remains a relatively new field, and CER-specific research methods are still in development. Commonly used methods are based on classic study designs and include those listed in Box 15.1.

Though the randomized effectiveness trial (i.e., “pragmatic” RCT) is the method of choice for studying the effectiveness of an intervention, as it would perform in the real world, the associated challenges remain, such as high costs, long study duration, and need for large study populations. Examples of pragmatic RCTs in dermatology include a Dutch study of home versus outpatient ultraviolet B phototherapy for psoriasis (PLUTO) [5] and a UK study of prophylactic antibiotics for prevention of cellulitis (PATCH II) [6]. The PLUTO study is a noninferiority trial that was designed to determine whether or not home phototherapy is worse than

outpatient phototherapy. This study is notable for its broad inclusion criteria and lack of fixed phototherapy protocol which also allowed for initiation of other medications as clinically necessary – both key characteristics of a pragmatic trial as discussed in detail later in the chapter. The PLUTO study found home phototherapy to be equally as effective and safe as outpatient phototherapy, and home phototherapy was associated with greater patient satisfaction. The PATCH II study similarly exemplified characteristics of a pragmatic trial but also experienced slow patient recruitment and a diminished sample size, demonstrating the logistical challenges of conducting RCTs.

Considering the challenges of RCTs, nonexperimental/observational studies remain an important tool for CER and are estimated to represent approximately 80% of current CER efforts, at least in the USA [7]. Observational studies provide the advantages of being less costly and time intensive (particularly if retrospective in nature), being more reflective of the real-world clinical setting, and providing a resource for information about treatments, such as adherence, use of concomitant therapies, and effects of treatment selection, among others. For example, in a cross-sectional study of the effectiveness of commonly used therapies for moderate-to-severe plaque psoriasis using data from the Dermatology Clinical Effectiveness Network ([www.dermcern.org](http://www.dermcern.org)), comparisons of adalimumab, etanercept, ustekinumab, and phototherapy with methotrexate suggested that the effectiveness of psoriasis therapies in clinical practice is not as high as what is reported in clinical trials [8]. However, the cross-sectional nature of the study rendered it susceptible to potential bias due to clinical drift. Clinical drift may result in overestimation of the effectiveness of therapies, as only patients with good responses will continue their particular therapies.

The potential for introduction of such biases (i.e., selection and information bias), which limit internal validity, is just one example of why observational studies tend to be the subject of criticism. Other reasons for criticism include the heterogeneous nature of observational studies and the analytic challenges created by use of a heterogeneous study population. To address these concerns, new epidemiologic methodologies, such as propensity scores and instrumental variables, which will be described later, have been and continue to be developed to strengthen the quality of observational studies for CER [4].

## Assessing the quality of comparative effectiveness research

A thorough discussion of quality assessment for all possible study methods available for CER is beyond the scope of this chapter. As pragmatic RCTs are the gold standard for effectiveness research and observational studies are the most commonly utilized for CER, our discussion will be limited to these two study methods and will also focus on those topics that are especially relevant to CER.

### What makes a good randomized clinical effectiveness trial?

RCTs can be broadly categorized as efficacy or effectiveness trials, sometimes also referred to as explanatory or pragmatic trials, respectively [9]. Explanatory trials are designed to determine the effects of an intervention under ideal circumstances and are most relevant to answering a specific research question about the benefit of a medical intervention. Pragmatic trials, on the other hand, are designed to determine the effects of an intervention under the

**Table 15.1** Differences between efficacy and effectiveness research.

<b>Efficacy</b> How well does the intervention work in the ideal setting?	<b>Effectiveness</b> How well does the intervention work in the real world?
<ul style="list-style-type: none"> <li>• Stringent patient selection criteria to optimize safety.</li> <li>• Highly motivated patients with strict adherence to research protocol.</li> <li>• Highly trained investigators with expertise in the study drug.</li> <li>• Clinical response determined at arbitrary “short-term” time point.</li> <li>• Maximized internal validity.</li> </ul>	<ul style="list-style-type: none"> <li>• Heterogeneous patient population more susceptible to adverse events.</li> <li>• Variations in patient motivation and ability to adhere to prescribed regimen.</li> <li>• Variation in experience and knowledge of the drug by prescriber.</li> <li>• Clinical response determined in routine clinical visits.</li> <li>• Maximize external validity.</li> </ul>

### Box 15.1 Study designs for comparative effectiveness research

- 1 Experimental studies** (e.g., RCT). Experimental studies involve an active intervention to test a hypothesis. Of particular focus in CER is the design of RCTs that are more reflective of the real-world clinical practice, sometimes referred to as “pragmatic” RCTs. This includes head-to-head trials that compare more than one active intervention and use broadly representative study populations with less restrictive inclusion and exclusion criteria to maximize external validity.
- 2 Nonexperimental or observational studies** (e.g., cohort, case-control, cross-sectional). Observational studies do not involve an active intervention but rather rely on simple observation of events that occur in regular clinical practice in either a prospective or retrospective manner.
- 3 Research synthesis** (e.g., systematic review, meta-analysis). Research synthesis involves a summary of multiple existing studies to address a specific common question.

conditions in which it will be applied in the clinical setting and are, thus, the design of choice for CER [10]. In addition to the basic quality assessments of an experimental RCT, which are discussed in Chapter 9, there are several other domains that have been previously identified to be important to assess in a pragmatic trial, as summarized in Box 15.2 [11,12].

In an optimal setting, a pragmatic trial adheres to all of the characteristics listed in Box 15.2. In reality, however, few trials can be defined as purely explanatory or pragmatic and instead display a mix of characteristics. As such, tools have been developed to help classify trials as explanatory or pragmatic, including the tool by Gartlehner *et al.* [12] and the Pragmatic–Explanatory Continuum Indicator Summary tool by Thorpe *et al.* [11]. Additionally, guidelines for quality reporting of pragmatic trials have been developed as an extension of the Consolidated Standards of Reported Trials statement for RCTs [13].

### What makes a good comparative effectiveness research observational study?

Observational studies are generally considered inferior to experimental studies because of their poor internal validity due to lack of randomization which leaves them susceptible to bias (systematic error) and confounding (“a mixing of effects”). However, observational studies can be powerful tools for CER when utilized properly and with recognition of their limitations. Systematic error (i.e., selection and information bias) and confounding in observational studies may be addressed by a number of methodologic designs (such as exclusion, matching, restriction of study subjects) or by statistical analyses (such as restriction, stratification, mathematical modeling). The quality of observational studies depends on use of these strategies to ensure the study results are not meaningfully influenced by systematic error and confounding.

#### Box 15.2 Characteristic domains of a pragmatic trial

- 1 *Participant eligibility criteria:* Eligibility criteria are generally less strict than those of an explanatory RCT, and all participants who have the condition of interest are enrolled.
- 2 *Experimental intervention flexibility:* The experimental intervention is applied under flexible conditions to reflect clinical practice.
- 3 *Comparison intervention:* The comparison intervention is represented by “usual practice” or the best available alternative method that may include the option of “watchful waiting.”
- 4 *Experimental and comparison intervention practitioner expertise:* The experimental and comparison interventions are applied by a variety of practitioners under various clinical settings.
- 5 *Follow-up intensity:* There are no formal follow-up visits except for those required for usual clinical care. The outcome of interest is identified by administrative database search.
- 6 *Primary trial outcome:* The primary outcome is an objectively measured, clinically meaningful outcome to the study participants that does not require special testing or training.
- 7 *Participant compliance with the “prescribed” intervention:* There is no active measurement of compliance. No special strategies to maintain or improve compliance are used.
- 8 *Practitioner adherence to study protocol:* There is no active measurement of adherence. No special strategies to maintain or improve adherence are used.
- 9 *Analysis of primary outcome:* The analysis includes all patients regardless of compliance, eligibility, and other factors in a manner that is analogous to the “intention-to-treat” analysis.

Source: Thorpe *et al.*, 2009 [11]. Reproduced with permission of Elsevier.

Several tools have been developed to measure the quality of observational studies [14]. Unfortunately, no gold standard for quality measurement exists, and none of the existing tools have been fully validated. As a result, there is little agreement upon which tool, if any, should be used to assess observational study quality. There are, however, agreed-upon guidelines for the reporting of observational studies. These guidelines are discussed in the Strengthening the Reporting of Observational Studies in Epidemiology statement, which includes a checklist of items that should be addressed in all observational studies [15].

### Specification of study design

The study research plan should be detailed in the methods section with clear definitions of study purpose, hypothesis, study population and individual patient characteristics to be collected, intervention and comparators, outcomes, and benefits and risks to be measured.

#### Study population

The study population should be generally representative of the setting in which the intervention is to be applied. An important design to be aware of and assess for is the “new user design,” also known as an inception cohort. The new user design only includes those subjects who have never previously received the intervention of interest. It is the study design of choice because the inclusion of prevalent users may introduce a “healthy user” effect that falsely overestimates the effectiveness or safety of an intervention [16]. The new user design most reliably captures the full effects of an intervention by avoiding selection bias that can be introduced by including prevalent users who may have already survived past a certain time risk window for the outcome of interest, thus leaving fewer remaining high-risk subjects (a process termed the depletion of susceptibles).

#### Study intervention and comparators

The experimental intervention should be compared with an intervention that is reflective of usual care in the real-world clinical setting and may include the option of “watchful waiting” if clinically appropriate. Use of multiple comparators is preferable over a single comparator. The interventions should generally be commonly used and preferred interventions of medical providers or patients.

#### Study outcomes (effectiveness, benefits, risks)

The outcome should be relevant to stakeholders and provide evidence that will assist with medical decision-making or resource allocation. Direct clinical outcomes (e.g., mortality) are preferred over intermediate or surrogate endpoints (e.g., serum biomarker). However, in situations where measurement of the direct clinical outcome is prohibited by time, relevance, or cost, surrogate endpoints may be considered when there is a previously established direct relationship between the surrogate endpoint of interest and direct clinical outcome. In dermatology, where measurement of a direct outcome such as survival is not always relevant, outcomes should be prioritized according to stakeholder input and preference in order to maintain clinical relevance.

### Study conduct, analysis, and reporting

#### Data collection

For observational studies, data may be collected primarily (i.e., collected specifically for the study) or secondarily (i.e., collected for other purposes). With primary data collection, care must be taken

in the study design so as not to affect the usual medical practices of the health care provider. With both primary and secondary data collection, a thorough understanding of the data source is required to avoid introduction of bias and false interpretation of results.

### Data analysis and interpretation

Since observational studies are nonrandomized, data analysis should include methods to account for different subject characteristics among the comparator groups that may be associated with the study outcome (i.e., confounding). Methods to control for measured confounding factors include stratification, restriction, and matching according to the confounder as well as statistical methods to adjust for confounding. Unfortunately, it is not possible to measure all potential confounding factors, and residual unmeasured confounding may also impact the results in a manner that can be difficult to predict. To understand the potential effects of unmeasured confounders on the outcome, sensitivity analyses can be performed to estimate the effects of individual unmeasured confounders at various prevalence levels on the outcome of interest [17]. Any observational study should include at least one of these methods to manage confounding variables. If confounding is not accounted for in the study design or analysis, final effect estimates are referred to as “unadjusted” measurements and are likely to represent false associations in either the positive or negative direction.

When assessing observational studies, there are two main types of biases of which to be aware: information bias and selection bias. A thorough discussion of bias in observational studies is beyond the scope of this chapter, and the reader may refer to other resources for more information [18–20].

Of particular relevance to CER is a special form of selection bias called confounding by indication or channeling bias. Channeling bias specifically refers to the differential allocation of an intervention according to a subject’s likelihood of developing the outcome of interest. As a hypothetical example, in an observational study of adverse hepatic effects from methotrexate treatment of psoriasis compared with other systemic treatments, channeling bias may be introduced by the fact that dermatologists are more likely to prescribe methotrexate to patients with low baseline risk of developing hepatic complications.

Channeling bias may be addressed by several aspects of study design or statistical analysis, including controlling for known prognostic factors for the development of the outcome of interest and methods similar to those used to adjust for confounding variables, including matching, stratification, and restriction. Two newer methods that have been developed to address channeling bias include the use of propensity scores and instrumental variables.

Propensity scores measure a subject’s likelihood to receive a particular intervention and may be used to match subjects who are similarly likely to receive the interventions being compared [21]. Instrumental variables are factors that affect the outcome through an association with the intervention but have no independent effect on the outcome. Advanced statistical methods can be used to adjust for instrumental variables [22]; however, such methods are complex, and identification of a true instrumental variable is not necessarily easy. As an example, in a study comparing the effect of exposure to cyclooxygenase-2 inhibitors versus nonsteroidal anti-inflammatory drugs on gastrointestinal complications, an instrumental variable is the physician’s prescribing preference for one drug over another [23].

It is essential that every study include a discussion of potential biases and how they may affect the reported results in order to

guide the interpretation of the study findings. Even the most well-conducted observational studies and observational studies that use complicated analytic methods cannot be free of all biases. However, when appropriate study design and statistical methods to minimize confounding and bias are used, observational studies and RCTs across a number of research topics have been found to exhibit very good correlation, with only 16% of studies indicating significantly different summary results [24].

### Guidelines for reporting of observational comparative effectiveness research

New methodologies are being developed to address the particular challenges of CER, and guidelines for performance and assessment of comparative effectiveness studies are continuing to evolve. For more detailed discussions of recommended research practices, the International Society for Pharmacoeconomics and Outcomes Research has published a series of good research practices of observational CER studies using secondary data sources [25–27]. Because CER is a relatively new research field, validated tools for quality assessment for observational CER studies do not yet exist. However, the Good Research for Comparative Effectiveness (GRACE) principles – an accepted hierarchy of evidence and key elements of good research practice for observational CER studies – with an accompanying checklist have been compiled by the GRACE Initiative, a group of international experts in the field of pharmacoepidemiology, and are supported by the International Society for Pharmacoepidemiology (<http://www.graceprinciples.org/>). The purpose of the GRACE principles is to aid in the assessment of observational comparative effectiveness studies and may be referred to for more detailed information.

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# Outcome measures

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## Introduction

Engaging a patient in a therapeutic process involves assessing one or more outcomes. On an everyday basis, physicians and patients use outcome assessment instinctively, in the same way that Molière's Mr Jourdain was speaking in prose without knowing it. Asking a patient how they are feeling after the first 3 months of their treatment is outcome assessment. Here, the outcome evaluation has the advantage of being very feasible, almost universal, and suitable for many diseases and many patients. More specific outcome measures are also used routinely, generally, in nonstandardized ways.

In contrast, when a treatment is evaluated in a clinical trial, trialists go into great detail about outcome selection and outcome measurement. Several different outcomes are used in a given trial in order to evaluate the multiple facets of disease change. And the procedure of outcome measurement is (or more realistically *should be*) precisely documented. In a controlled trial, it is crucial to isolate one of the outcomes as the *main outcome*. The main outcome has to be the most relevant outcome regarding the study's main objective. It is used to calculate the sample size, and the fate of the trial rests on the result of the statistical test performed on the main outcome.

In the following sections, we will discuss several aspects in the "life" of an outcome, from the "producer" to the final user. Our emphasis and examples will be on clinical outcomes, but almost all the commentaries may apply to other types of outcomes; for example, radiology-based, pathology-based, or biological outcomes. Moreover, most of the elements are discussed in the context of clinical research.

## What can we do with outcomes?

### Elaborate

Many outcomes are based on scores measured on scales. Psoriasis area and severity index (PASI) is a well-known scale used in psoriasis research, and also used in routine patient care. The score is based on a semi-quantitative assessment of erythema, thickness, and scaling in four body areas. Numerical expressions of these

semi-quantitative assessments are then mathematically combined with categories of surface assessment to yield a score from 0 to 72. Examples of other scales used in dermatology include scoring atopic dermatitis (SCORAD), six area six signs atopic dermatitis (SASSAD), score for toxic epidermal necrosis (SCORTEN), and vitiligo disease activity (VIDA). There are many others.

An important point is to make the distinction between a scale (yielding a score value) and an outcome. For example, whereas PASI is a scale yielding a score, the "percentage of patients whose final PASI score value is less than 75% of their baseline PASI score value," commonly abridged as "PASI75," is an outcome, based on the PASI score. Another PASI-based outcome would be the percentage of PASI score improvement from baseline.

In a research paper assessing the type of outcome and the quality of outcome reporting, we proposed a typology of outcome construction by addressing three questions, and we formed the acronym "VIP," in which V stands for variable, I for items, and P for time-points [1]. The V question is about the type of variable for the assessment of the outcome at the group level (quantitative or qualitative – usually binary). The I question distinguishes collections of several individualized items (e.g., erythema, scaling, thickness, for PASI) from a collection of a unique item (or a global evaluation). The P question refers to whether the outcome is based on a collection of information made at the final point or on both initial and final points. Table 16.1 presents the breaking down of some outcomes with the VIP questions and demonstrates how different outcomes can incorporate the same scale.

This framework is useful to construct most of the outcomes. The way the information is collected is discussed further in the "Assess (measure)" section.

### Evaluate

Because outcomes are based on some kind of measurement, one should ideally be able to describe the qualities of the measurement. A measurement should perform well regarding three main characteristics: reliability, validity, and sensitivity to change [2].

Reliability, also called precision, reproducibility, and consistency, deals with the following question: Does the measure give the same



**Table 16.1** Examples of different outcome constructions (“VIP questions”: V, variable; I, items; P, time-points; see text).

Disease	Primary outcome as stated	Variable		Item		Time-point		Comment
		Type of final variable (used in the statistical analysis for a patient in each randomized group)		Method of data collection: multi-items vs single item or global evaluation		Time-points of patient assessment		
		Type	Explanation	Type	Explanation	Type	Explanation	
Psoriasis [9]	Percentage of PASI reduction from baseline to 12 weeks	Quantitative	Percentage of PASI reduction from baseline to 12 weeks	Multi-items	PASI (erythema, scaling, thickness, surface)	Initial and final	PASI at baseline and at 12 weeks	In the same article, the secondary outcome was binary: the proportion of persons with 75% PASI reduction
Atopic dermatitis [8]	Response rate at day 21	Binary	Response was defined as at least 60% reduction in the mLEASI	Multi-items	mLEASI (erythema, infiltration, excoriation, and lichenification)	Initial and final	mLEASI at baseline and at 21 days	
Bullous pemphigoid [9]	Disease control at day 21	Binary	Disease control at day 21 was defined as the absence of new bullae for the last three consecutive days	Single item	Number of new bullae	Final only	Number of new bullae on the last 3 days	
Cetuximab-associated acne-like eruption [14]	Lesion count at completion of treatment	Quantitative	Number of lesions	Single item	Lesion count	Final only	At the end of the treatment	

mLEASI: modified local eczema and severity index.

value each time it is measured? Reliability is affected by random error. Depending on the research questions, the main source of variability is between patients or between physicians who have rated the patients. Therefore, reliability is assessed as the consistency of repeated measurements by a single observer on a sample of subjects (intraobserver reliability), and by different observers performing measurements on the same sample of subjects (interobserver reliability).

Accuracy deals with the following question: Is the measure truthful, and does it measure what is intended? Accuracy is affected by systematic errors. A systematic error could be the result of observer bias, subject bias, or instrument bias. The accuracy is best assessed by comparing the measure with a gold standard; that is, a reference considered to be accurate. For most dermatological diseases no concrete gold standard exists; therefore, to assess how well the measurement represents the phenomenon of interest the convergent validity could be used. Convergent validity is the degree to which a measure is similar to (converges on) other measures that it theoretically should also be similar to. Other components of validity, such as face validity, are used to assess validity of a new instrument.

Sensitivity to change deals with the following question: Does the measure discriminate between the situations of interest? To obtain insight into the sensitivity to change, the scoring system should be assessed at baseline and during follow-up. Furthermore, effect size should be calculated. Therefore, agreement (reliability) between two observers on progression or regression in individual patients (Tx – T0 data) should be assessed. The percentage of patients with any change from baseline and the percentage of patients with clinically relevant change should be provided. It is important to know what constitutes the minimum clinically important change. Because such a definition is rarely available, a first step is to determine the smallest detectable difference that can be measured. A useful tool is one that detects clinically relevant changes rather than small changes.

Besides reliability, validity, and sensitivity to change, feasibility is an important dimension to take into account. Acquiring information on these parameters is done by performing studies dedicated to their evaluation. Those studies should be conducted on an appropriate sample of diseased patients in order to avoid spectrum bias and to guarantee acceptable external validity.

A “validated” instrument is an instrument for which all these important characteristics have been evaluated. Properly validated instruments with satisfactory qualities are rare, even in fields where scores are widely used, such as atopic dermatitis and psoriasis [3–6].

## Select

Outcome selection is driven by the objective(s) of the study. Several outcomes are usually necessary to capture the complexity of disease change. Classifications may be useful in order to select several dimensions of disease evaluation. There is no widely accepted typology of outcomes. They may be classified from the most objective ones (e.g., death, laboratory value) to the most subjective ones (e.g., pain intensity). The importance of incorporating patient-reported outcomes in any clinical research is increasingly recognized [7].

Using several outcomes has one main drawback, however. Making multiple comparisons between groups, as is usually the case in clinical research, increases the risk of falsely concluding an association (alpha-risk). Therefore, a hierarchy between the several selected outcomes must be set in advance, by isolating a “main” or “primary” outcome. The other outcomes are qualified as secondary outcomes. The primary outcome, with some acceptable exceptions, should be unique. In clinical research, the main outcome is supposed to be the most relevant outcome regarding the main objective of the research. Two additional qualities are required: first, the main outcome – but also secondary ones – must be clearly defined with no ambiguity in its entire definition; second, the way to express it, should be meaningful and “speak” to the end-user of the results.

Some effort is needed to improve outcome measurement in dermatology clinical research. In a systematic review of randomized trials dedicated to inflammatory skin diseases, 32% of 122 published articles had severe defects in those basic requirements [1].

The practice of using several outcomes has another drawback. Since there are large numbers of scales and their integration into outcomes, it is not uncommon that two trials on the same disease do not have even one outcome in common even though they may intend to assess the same domains. Between-trials comparisons of results are hampered by this inconsistency, as is synthesis of study results in systematic reviews and meta-analyses. These issues could be addressed through the development of an agreed-upon standardized collection of outcomes, known as a “core outcome set,” which should be measured and reported in all trials for a specific clinical area. The Core Outcome Measures in Effectiveness Trials initiative provides researchers with methodological resources to pursue the path to consensus rigorously [8]. In dermatology, the Harmonising Outcome Measures for Eczema (HOME) initiative is underway to select a core outcome set for atopic dermatitis [9].

### Assess (measure)

Once the outcomes have been elaborated, precisely defined, evaluated (ideally), selected, and hierarchized, the conditions for collecting data must be defined. In the context of clinical research, all these conditions must be clearly stated in the protocol, leaving no room for personal interpretation. A useful guidance is to follow the simple systematic questions of who, what, when, where (why), and how. We have proposed gathering all the elements defining an outcome, including its “VIP” structure and the conditions for collecting information, under the mnemonics “Kipling’s six honest serving-men and the blind VIP” (Box 16.1) [1].

One condition, requiring specific attention, is blinding. Together with randomization, blinding can be considered the most important pillar in the methodological architecture of therapeutic research [10,11]. The “double-blind” design refers to the patient and the care-provider being unaware of the assigned treatment. The “triple-blind” expression usually refers to the blinding of the statistician during the analysis. However, double-blind designs cannot always be implemented for practical or ethical reasons. Even in these situations, it is often possible, when the assessor is not the patient, to implement conditions for a blinded assessment. It may necessitate the use of a third party; for example, a physician who is not involved in patient care. Blinded assessment of the outcome is key to lessen bias in trials [12].

### Analyze

Analyzing outcomes is usually straightforward, provided that outcomes have been unambiguously defined. The statistical methods to be used depend on the types of variables but are out of the scope of this chapter. In some instances, the comprehensive definition of the outcome may lead to choosing between several types of analysis. For example, a proportion of patients reaching complete remission can be analyzed at multiple time-points (analysis of censored data) or at a fixed final time. More generally, if an outcome is selected at multiples times during follow-up, the time for the main analysis should be stated in advance since multiplying statistical tests inflates alpha-risk.

### Report

Reporting of outcome results should be complete. A complete outcome result for a randomized trial should include the value of

#### Box 16.1 Checklist proposal for the (primary) outcome description

##### Kipling’s six honest serving-men and the blind VIP

##### 1 Kipling’s six honest serving men\*: why, what, when, where, who, and how?

*Why* was this outcome chosen as the *primary* outcome?

*What* was the supporting “material” (e.g., photographs, lab result, patient)?

*When* was the final evaluation made (including serial evaluation in censored data analysis)?

*Who* made the evaluation (e.g., the treating physician, one or more independent evaluator(s), the patient, an automatic device)? If several evaluators were required, was a harmonization process implemented? How were conflicted evaluations on the same material handled?

*Where* was the evaluation made (usually the setting of the trial)?

*How* was the evaluation made; that is, any process used for collecting the elementary items used for the outcome construction. If several items had to be combined, how was that done; that is, using what algebraic or logical rule?

##### 2 “Blind”

Any procedure for implementing blinding should be described. Any procedure to evaluate the quality of blinding should be presented. Non-blinding during evaluation of the outcome conveys a risk of biased assessment.

##### 3 The three “VIP” questions for outcome construction

The three “VIP” questions (“Variable,” “Items,” “time-Points”) may appear as technical ones, but any clear description of an outcome allows rapid and unambiguous answers to these questions:

(a) What type of variable is attributed to a patient? (Binary, quantitative, other?)

(b) What type of information is collected? Multiple items? Single item? Or a global evaluation?

(c) What time-points are used to define the final outcome? Is the initial state a component of the final evaluation (“Initial and final time-points” versus “final only time-point”-based outcome construction). “Direct assessment of change” is a special case based on the contemporary assessment of both initial and final state.

\* Refers to Rudyard Kipling’s poem “I keep six honest serving-men”, *The Elephant’s Child, Just So Stories* (1902).

Source: Nassar *et al.* 2012 [1]. Reproduced with permission from *Nature*.

the outcome in each group (summary value and dispersion) and the result of the statistical test that compares those two results. An isolated mention of the degree of significance is not sufficient since it does not give an idea of the magnitude of the absolute value in each group and their relative differences. In the method section, the reporting of the definition of the outcomes and of the conditions of their measurement should be precise enough to answer all of the questions from the checklist “Kipling’s six honest serving men and the blind VIP” (Box 16.1).

Outcome reporting bias has emerged as a pervasive source of bias. Outcome reporting bias consists in not reporting the result of the primary outcome or post-hoc change for the primary outcome. Changes occur after trial completion and are oriented by the knowledge of the more favorable results. Changes may relate to the definition, the selection (outcomes not reported), or the hierarchy (a secondary outcome becoming the primary one) of outcomes [13–16].

### Criticize and use

All the preceding steps are meant to be critically assessed, with the main question in mind being “Is this result relevant to my practice

and my patient(s)?". Of course, this question implies focusing on more than just the outcome and demands that one critically appraise the study's objective, potential sources of bias, and external validity. Regarding outcomes, the main question is usually about relevance in the outcome selection and construction and, finally, appraising the importance of the difference between groups from a clinical perspective.

## Outcomes in dermatology and future directions

The number of skin diseases is impressively high with a great variety in expression. Patients' complaints and diagnostic analysis mainly rests on visible lesions, translating in a majority of outcomes being based on clinical examination. Clinical outcomes are less objective than radiology-based or laboratory-based outcomes, and therefore easier to create and modify. This contributes to the large array of scales and scores being available. One important challenge for dermatologists is to organize (as is underway for eczema with the HOME initiative) the selection of core outcome sets, disease by disease [9]. Another challenge, not specific to dermatology, is to think about outcomes and trials designed to compare treatment strategies, in order to assess effectiveness and tolerance in the long run for chronic diseases, rather than comparisons of efficacy for individual drugs in the short term.

The technical progress in photography and the shift to digital photographs make storage and transfer of images easy. This technological advance makes it possible to reassess and verify observations using images and, thereby, increases the number of assessors. Some practical obstacles persist; for example, standardization may be difficult to implement. Technical progress may overcome these difficulties soon, and we may have to rethink the construction and assessment of dermatological clinical outcomes based on these new technical possibilities.

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# Where does qualitative research fit into evidence-based dermatology?

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## Definitions

Qualitative research aims to gather an in-depth understanding of human behavior and the reasons that govern it. Researchers who use qualitative methods aim to “study things in their natural setting, attempting to make sense of, or interpret, phenomena in terms of the meanings people bring to them” [1], and they use “a holistic perspective which preserves the complexities of human behavior” [2].

Qualitative methods investigate the *why* and *how* of decision-making. They provide an opportunity to look deeply into the human illness experience by focusing on meanings, concepts, characteristics, metaphors, and symbols provided in the patient's story. It is about sensitivity to the nuances of that narrative. What is it that those encountering skin symptoms believe is wrong with them? How initially do those experiencing skin symptoms deal with it all? What exactly indeed do they *do*, as a result of their illness and all that goes with it; that is, what form does their illness behavior take? Has the advent of the internet made a difference, and if so how? Questions like these are the ones addressed by qualitative research.

## Qualitative research and evidence-based medicine

“... he was moribund and screaming . . . I examined him. He had obvious gross bilateral cavitation and severe pleural rub. I thought the latter was the cause of the pain and screaming. I had no morphine. . . I felt desperate. I knew very little Russian then . . . I finally instinctively sat down on the bed and took him in my arms, and screaming stopped almost at once. He died peacefully in my arms a few hours later. It was not the pleurisy that caused the screaming but loneliness. It was a wonderful education about the care of the dying . . .”

This passionate account comes from Archie Cochrane, one of the founding personalities of evidence-based medicine [3]. There are at least two components to any medical encounter, the relational one and the technical one. These two components are acknowledged in the definition of evidence-based medicine itself which states “the

conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” The patient's values, characteristics and circumstances matter in these decisions.

In spite of such considerations, emphasis in evidence-based medicine is usually given mainly to the technical aspects. Traditionally, clinical research has been characterised by a reliance on quantitative methods directed towards the generation of “hard” numerical data relevant to clinical practice. There has been an emphasis on aiming for narrowness and closeness of focus, precision, control and replicability; the application of statistical analytical techniques; and efforts to generate causality statements and “explanation”. With the emergence in medicine (or re-emergence since Hippocrates) of a model bringing together the biological and the psychosocial, the contribution of a qualitative approach integrating with quantitative evidence, has been advocated [4]. Examples are drawn from a few areas.

## Measuring disease

Attempts at the development of instruments for measurement and scoring systems have become a key feature of modern medicine. One example has been the ubiquitous reliance in research into psoriasis on the psoriasis area and severity index (PASI). Critics have of course pointed to the fact that in this important instance numerical scores have simply been accorded to subjective judgments of *severity*, bringing an appearance of objectively reliable data which is at least questionable. Undoubtedly, merging attempts at formal assessment and measurement of current severity via PASI (or similar) and life impact via dermatology life quality index (DLQI) with individual case analysis and qualitative data relating to lifetime experience would enhance the value of research. The complexity of interconnected symptoms of varying, fluctuating severity, individual adjustment, public response and coping behavior, all located within their “natural” setting rather than the artificial circumstances of the clinic, need to be investigated. In particular, the vital importance of a long-term perspective cannot be overstated since the most common major skin disorders are



characterized by extended chronicity [5]. Patients themselves (perhaps especially older psoriasis patients and/or those with an extended course of illness) may surprise their doctors for example by refusing a new or more zealously assertive therapy, preferring less or even no treatment at all, setting their current circumstances including their symptoms in the context of their own long experience of the disease and its treatment [6]. Instruments like the DLQI rely upon a few limited questions concerning recall of very recent life events, within the last month at the longest. In-depth interviews and other qualitative methods and analysis have suggested, however, that what matters to patients and influences their own judgment of the severity of their condition can be dramatically different from those formally measured by PASI/DLQI [7,8]. Sadly, there is all too little research evidence, and scarcely any that deals satisfactorily with cross-national or cross-cultural differences.

### Behavioral effects of disease and treatment

Human beings subjectively attribute meanings to their experience, drawing more or less, for better or worse on the resources made available by the culture surrounding them, their place in society and the social groups to which they belong. They make sense of and interpret what is happening around them, and attune more acutely to those that appear to be directly important to them. Their circumstances can and do naturally change, demanding dynamic responses across the life cycle for example but also day to day in a less organized and structured fashion. People react and act accordingly. The experience of illness, not only the underlying organic disease and the psychosocial organization and requirements of it and its treatment inevitably affects behavior, and potentially chronic dermatological illness can have life-long impact. Treatment regimens which are founded on a basis of scientific enquiry and understanding and the subjective beliefs, perceptions and judgments of clinicians will have a crucial role [9–12]. Therapy organizes, at times perhaps determines the form and content of the patient's experience of the illness. Those affected must make sense of it, and all that is entailed in terms of psychological and social consequences within the wider context of their lives. It is a reflexive process in that the illness, treatment, and behavioral accommodation within unfolding social circumstances and contingencies, will all interact and feedback in a subtle fashion [9,10].

### Stigmatization and coping

Fundamental questions are being posed for those affected: "What is happening to me? What do these experiences, feelings and events mean? In particular what does it all mean for me and my life? What can I do? What should I do, when, how, with what guidance if any, from whom?" Thus, there is more to skin disease than mere disease of the skin. It goes beyond biological disorder and dysfunction [11,12]. There are psychological, social, cultural, and economic dimensions, and also political factors which shape decision-making by those who fund or provide professional services thereby affecting the character, shape and substance of dermatological care [13].

Diseases like acne, eczema, vitiligo, and perhaps distinctively and notably psoriasis, do not manifest themselves simply as organic disorders. They also have a historically longstanding place in the public consciousness, constituting significant *social representations*, which involve imagery, ideas, perceptions, beliefs, attitudes, explanations and judgments [14]. They are elaborate social constructs built up over generations, constantly elaborated, amplified and reinforced in public discourse and social interaction. Therapeutic modalities constitute an important element, and historically they

have been a cumbersome burden to patients [15–18]. The adverse implications for affected individuals and indeed for those who seek to offer them support can amount to serious handicap [19]. They should be neither ignored nor dismissed. Thus stigmatizing social representations and connotations are a central feature and crucially important component of psoriasis as an illness and as a cultural and social phenomenon. Explanations of the processes of stigmatization founded solely upon biological thinking, study and analysis are likely to be unconvincing, whereas the conceptual and interpretative tools of the social sciences offer considerably more promise.

### Preferences and treatment adherence

Public and patients alike can remain stubbornly resistant to professional perspectives and persuasion; and medicines-use-behavior, for example, can be deliberately based on the exercise of choices at odds with medical advice and directions, in disregard of efforts to modify and "correct" them. Limited adherence is common [20–22]. Such behaviors must be seen and understood within the frameworks of meaning and understanding which patients bring to their treatment, together with the social and economic contingencies bearing down upon their lives. However, many studies of "compliance"/adherence behavior and related short-term cognitive/behavioral interventions designed to secure strict conformity to the demands of therapeutic regimens currently favored by health professionals, abstract particular specific behaviors from their wider meaningful context within an illness career spanning decades.

### Communication skill and patient narratives

For patients, narratives may provide important ways of communicating their experiences, expectations, hopes, doubts, pain, frustrations, joys, and needs. The organization of patients' narratives into a database has been attempted as a means to describe the widest practicable range of individual experiences from the patients' perspective [23,24]. Personal narratives presented without attempts at more formal analysis, may offer both data and insights worthy of attention for the qualitative experiential evidence they provide. There is much to be learned, for example, from revealing reflections by major authors who have experienced psoriasis and its treatment, presenting them in fiction, autobiographical accounts or media interviews. From the USA, John Updike gave telling accounts of the stigmatizing potential of chronic psoriasis, the character and impact of psoralen and ultraviolet A (PUVA), and the distressing reality of the failure of treatment [25,26]. These, in effect, represent fine examples of *auto-ethnography* and offer valuable insights. The British playwright Dennis Potter likewise wrote and spoke about the impact of his severely disabling chronic psoriatic arthritis and the treatment he received for it, in not only emotionally moving terms but also with information, insight, and illuminative reflection that should inform research [27]. His *The Singing Detective* is also notable not only in its own right, but also for the wide response it provoked from the audience and the media, scrutiny of which generated data directly relevant to understanding the cultural representation of the disease, popular understanding and misunderstanding of it, and the elaboration of stigmatizing connotations [28–30].

### Health-care models and organization

There is good evidence that clinical decision-making in medicine, including dermatology, can be influenced, indeed be founded upon, considerations other than scientific evidence, which may include tradition, national and local custom and practice, individual prefer-



ence, the commercial interests of pharmaceutical companies, and economic or political constraints [18,31–33]. An integration of quantitative and qualitative research is obviously needed to inform the organization of health care, to identify gaps in the ways care is delivered, and to define health-care models [34]. Integration of quantitative and qualitative research is especially relevant when caring for patients with chronic diseases. In the so-called “chronic care model,” self-management integrates with the health system, capitalizing on interaction between an informed patient and a prepared proactive team [35].

To summarize, the *disease* at issue may appear to be the psoriasis or eczema of the medical textbooks, narrowly depicted and addressed in terms of the biological sciences. But revealed by the instruments of qualitative research, the *illness* involves much more. It is a complex social phenomenon. It is a construction embedded in long-established cultural representations providing a framework, a repertoire, to be drawn upon for values, beliefs, perceptions, attitudes, prejudices, preferences, and behavioral patterns relevant to the process of coming to terms with symptoms, therapy, and the social reception of both. It sits within an elaborate social organization of which the delivery of care is a component part. Research which takes the character and content of the world-view and behaviors of health-care professionals as most important, presumes them to be unproblematic, and focuses solely on the diseases of patients fails to pose important questions, obscures critical evidence, and inhibits understanding.

## Methods

Qualitative research methods are founded on the notion that behavior and events occasioned by the onset and course of disease can be understood only if they are seen in their context, holistically, grounded upon a detailed well-documented description [36,37]. Methods used may range from textual analysis of documentary sources and patient diaries, passive observation of patients’ behaviors in certain settings, participant observation where the researcher is both part of the clinical setting and is also simultaneously an observer, audio and video recordings, focus-group discussions, and “in-depth” interviews (Table 17.1). In-depth interviews may encourage patients to relate experiences about their illness, thereby constructing a personal illness narrative.

Quantitative research should begin with an idea (usually articulated as a hypothesis), which then, through measurement, generates data and, by deduction, allows a conclusion to be drawn. Qualitative research, by contrast, begins with an intention to explore a particular area, collects “data” (observations and interviews), and largely generates ideas and hypotheses from these through what is known as inductive reasoning. The strength of the quantitative approach lies in its reliability (repeatability) – that is, the same measurements should yield the same results time after time. The strength of qualitative research lies in its validity (closeness to the truth). By deploying an array of selected data collection methods, good qualitative

research should deliver penetrative insight, reaching the core of what is going on rather than just skimming the surface.

The validity of qualitative methods is greatly improved by using a combination of research strategies, a process known as triangulation, and by independent analysis of the data by more than one researcher. The so-called iterative approach, altering the research methods and the hypothesis as the study progresses (in the light of information gleaned along the way), used by qualitative researchers shows a commendable sensitivity to the richness and variability of the subject matter. Failure to recognize the legitimacy of this approach has, in the past, led critics to accuse qualitative researchers of continually moving their own goalposts. Though these criticisms are often misguided, it has been recommended that qualitative researchers must allow periods away from their fieldwork for reflection, planning, and consultation with colleagues.

## Critical appraisal and meta-analysis

There is no hierarchy of evidence among methodologies for qualitative studies. The units of analysis in qualitative papers are the findings, presented as themes, metaphors, or concepts as identified by the researchers. By its very nature, qualitative research is nonstandard [38], and it is debatable, therefore, whether an all-encompassing critical appraisal checklist could ever be developed. Even if such a checklist may not be as exhaustive or as universally applicable as the various guides for appraising quantitative research, it is certainly possible to set some ground rules (Table 17.2) [36].

The synthesis or “pooling” of the findings of qualitative research remains a controversial area. Some researchers contend that, because of the “subjective” and individual nature of human experience, the findings of qualitative research are unlikely to be generalizable, whereas others consider that the heterogeneity of ideological, or methodological, backgrounds of the different approaches in the area hampers combination. In spite of these negative views, some attempts to combine study results are acknowledged as crucial if the findings are to have impact in policy and practice of health care [34]. Unfortunately, there is no emerging consensus on appropriate guidance for the systematic review of qualitative evidence. The two dominant, opposing views focus on interpretation, as in meta-

**Table 17.1** Methods used in qualitative research.

- Ethnography, including auto-ethnography and case study
- Direct observation
- Participant observation
- Focus groups
- In-depth interviewing: (a) unstructured; (b) semi-structured
- Documentary analysis/content analysis

**Table 17.2** Critical appraisal of qualitative research studies.

- 1 Does the paper describe an important clinical problem addressed via a clearly formulated question?
- 2 Is a qualitative approach appropriate? Exploration, interpretation, deeper understanding versus quantitative estimations.
- 3 How were the setting and the subjects selected? Was there an “average” view of a patient population, or an in-depth understanding of the experience of particular individuals or groups?
- 4 What was the researcher’s perspective, and has this been taken into account? It is important to recognize that there is no way of abolishing, or fully controlling for, observer bias in qualitative research. It is important that they describe in detail where they are coming from so that the results can be interpreted accordingly.
- 5 What methods did the researcher use for collecting data – and are these described in enough detail?
- 6 What methods did the researcher use to analyze the data – and what quality control measures were implemented? Analysis of qualitative data can and should be done using explicit, systematic, and reproducible methods.
- 7 Are the results credible, and, if so, are they clinically important?
- 8 What conclusions were drawn, and are they justified by the results?
- 9 Are the findings of the study transferable to other clinical settings? One of the commonest criticisms of qualitative research is that the findings of any qualitative study pertain only to the limited setting in which they were obtained. In fact, this is not necessarily any truer of qualitative research than of quantitative research.

ethnography [39] versus integration/aggregation; for example, in the methods developed by the Joanna Briggs Institute [40]. The usefulness of meta-ethnography lies in its ability to generate theoretical understandings that may or may not be suitable for empirical testing. Meta-aggregation is the preferred approach for developing recommendations for action.

## Final remarks

Qualitative methods are designed to reveal and illuminate the subjective meanings people attribute to the experiences and events which impact significantly upon their lives. The findings generated by qualitative research should, for example, inform, enable, and enhance understanding of the natural realities of the experience of disease and its treatment, and the behaviors that both may elicit [41]. Qualitative enquiry can stand comfortably and usefully alongside quantitative research, perhaps suggesting and exploring questions which can then be addressed in ways delivering quantitative results; or coming from the opposite direction, quantified data may be the better understood if they provide a start-point basis for the *conversation* with respondents which is intrinsic to qualitative research.

Whereas to date, understandably, the focus of qualitative study in dermatology has been almost solely on patients in this regard (as it is of course in quantitative work), there is every reason for widening the investigative gaze in future studies to include scrutiny of the attitudes, beliefs, and decision-making built into the professional world of the medical practitioners they consult and who are so crucial to the determination of the *trajectory* of their illness – that is, its shape, length, and character [15,42–44].

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## Other useful resources

[www.healthtalkonline.org](http://www.healthtalkonline.org)

# Applying the evidence back to the patient

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## Introduction

Applying external evidence from published papers back to the patient is perhaps one of the most difficult and least discussed steps of evidence-based medicine (Figure 18.1) [1,2]. Having unearthed some relevant, high-quality and valid information from clinical trials in relation to a clinical question generated by a patient encounter, five questions now need to be asked in order to guide the application of such information to that patient [3]. They are listed in Box 18.1 and discussed in turn below.



**Figure 18.1** Clinical trial evidence is all very well, but what if the patient in front of you says, “I don’t want that treatment.” What then?

## How similar are the study participants to my patient?

### Trial participants are often different from clinic patients

Participants in clinical trials may be different from the patient who originally prompted you to ask an evidence-based question – in obvious biological ways such as age, sex, and clinical disease type [4]. In most circumstances, these differences do not prevent you

from making some useful generalizations from the literature. For example, you can generalize from a randomized controlled trial (RCT) of topical corticosteroids for atopic eczema in the absence of strict diagnostic criteria, provided that the description of that disease is consistent with atopic eczema – for example, with phrases such as “itchy red flexural eczema.”

Occasionally, the description of the clinical trial participants may render it difficult to extrapolate study results to the patient in front of you. For example, it may be unrealistic to generalize the results of an RCT dealing with high-dose ultraviolet A in the treatment of young women with an acute flare of atopic eczema to an older man with extensive chronic lichenified atopic eczema. In such circumstances, perhaps more weight should be given to one trial of chronic eczema in adult men than to several trials conducted in younger women.

Perhaps one of the most frequent problems encountered is that of having to generalize trials of adult therapy to children, in whom RCTs are rarely performed. Children are not simply miniature adults, especially when it comes to dosing of drugs, which is often best done by body mass index or surface area rather than weight. Yet children can suffer almost all of the “adult” skin diseases, and practitioners frequently have no choice but to use adult-based data as a guide.

Another difficulty is that treatments that appear promising when tested in enthusiastic and relatively healthy clinical trial volunteers often turn out to be less effective when applied to a wider group of patients with other comorbidities and levels of compliance. Such a divergence between study participants and real patients has been termed the difference between efficacy and effectiveness [5]. A regimen that involves applying creams three times a day may be attainable under the special conditions of a clinical trial, with continuous encouragement from the study assessors (and sometimes financial inducements). However, when it is tried by busy working individuals, it may simply be too much trouble. Such effects can often be explored by looking at the dropout rate for different interventions and reasons for such dropouts. Finding poor compliance rates due to an inconvenient treatment schedule should not deter the reader from using the evidence, but rather make one more aware of the factors that need to be taken into account when

**Box 18.1** Questions that need to be considered when generalizing from studies to a patient

**Are the patients in these trials sufficiently similar to mine?**

- Do they differ in certain biological characteristics, such as age and sex?
- Do they differ in terms of disease subtypes – for example, pustular versus plaque psoriasis?
- Are there social factors that may diminish compliance?
- Does the patient suffer from other comorbidities, such as renal disease?
- Does the patient have a similar baseline risk of benefit or adverse events as the trial participants?

**Do the outcomes make clinical sense to me?**

- If a composite scale of signs and symptoms has been used, do you know what it means?
- Has the scale been deliberately selected or modified to enhance the apparent treatment effect?
- Are the main outcomes measured at an appropriate time point – for example, months for a chronic skin disease, or days for an infectious one?
- Has the patient's views of treatment benefit been considered?

**Is the magnitude of benefit likely to be worthwhile for my patient?**

- In addition to seeing whether a treatment produces statistically significant gain over its comparator, is the magnitude of that gain clinically worthwhile?
- Does the patient consider the magnitude of gain adequate to justify the risk and expense?
- Have you translated the magnitude of benefit into the number needed to treat for that patient's baseline risk – do you still think it is worthwhile?

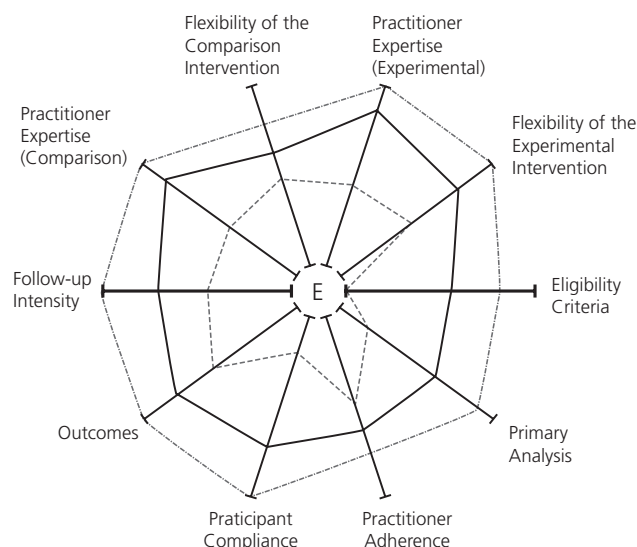
**What are the adverse effects?**

- Why did patients drop out of the studies?
- Have you considered rare side effects that might not show up in the trials?
- How will you communicate this risk of adverse events to your patient?
- How will you involve your patient in weighing up the pros and cons of the treatment choices?

**Does the treatment fit in with my patient's values and beliefs?**

- What is the patient's prior belief about the proposed intervention?
- Does the patient prefer a topical or systemic medication?
- Would the patient prefer no pharmacological treatment at all?
- What treatments has the patient had before?

describing the potential efficacy of a treatment to the patient. One type of trial design – namely, the pragmatic clinical trial – overcomes the “ideal patient” effect by recruiting as wide a mix of patients as possible and by capturing the effects of poor compliance in the final analysis [6]. Pragmatic clinical trials [7] are arguably the most informative type of clinical trial for generalizing to wider clinical populations, and examples of such trials may be found in dermatology [8,9]. The degree of pragmatism of a particular clinical trial can be estimated by means of a PRECIS (pragmatic–explanatory continuum indicator summary) wheel [10], which plots out the relative pragmatism for 10 different trial domains including eligibility criteria and follow-up intensity, as shown in Figure 18.2 for a trial of tetracyclines in bullous pemphigoid [11].



**Figure 18.2** PRECIS wheel showing the mean of the scores given by BLISTER trial management group members (solid line). Also presented are the most explanatory scores (inner line) and most pragmatic scores (outer line) given in each domain. Scores were plotted on the wheel using a simple picture editing program.

**Groups are different from individuals**

Even if the person in front of you is a woman with acute atopic eczema, the results of the trial may not translate into real clinical benefit to her, for several reasons. First, because the treatment effects reported in clinical trials – whether the outcome is a mean change in severity score or the proportion of people cleared – refer to *groups* of people. In a group of patients with a summary treatment effect such as a mean change in the scoring index of atopic dermatitis (SCORAD) of five points, there may be some individuals with score improvements of 10 or 15 points, some with changes of three or four points, some with no change, and possibly some whose disease has worsened. For example, closer inspection of the trial data on sildenafil (Viagra) for the treatment of erectile dysfunction [12] suggested that some men had all the fun! It follows that the patient sitting in front of you might benefit a lot or very little from the proposed treatment. Most trials in dermatology are underpowered to allow for subgroup analyses to determine which patients are most likely to respond well. Therefore, one sometimes has little way of knowing whether your patient will respond well or poorly apart from trying the treatment and seeing what happens. Similarly, telling your patient that “60% of patients on average clear with this treatment” may not be very helpful if the patient then asks, “Am I in that 60%, doctor?”

One way forward is to see whether treatment response varies according to different study subgroups. However, it is unusual for dermatology RCTs to be large enough to include such subgroup analysis, and care has to be taken to be aware of “data dredging” in studies with many subgroup analyses. Conducting a series of “*n* of 1” trials on a given patient may appear to be one way forward [13], but such an approach is only suitable for stable chronic diseases and for treatments that do not affect the response to subsequent treatments. Others have suggested sophisticated net benefit methods for estimating treatment effects for individual patients from clinical trial data [14], but such an approach is probably only



suitable for areas of medicine where huge amounts of trial data are available, which is not the case for dermatological diseases. Pharmacogenetic testing and biomarkers are other possible ways for predicting whether an individual will respond to a drug. For example, measurement of thiopurine methyltransferase levels predicts who will develop serious bone-marrow suppression from oral azathioprine [15]. Such stratified medicine using point-of-care testing is likely to play an increasing role in medical decision-making in future.

### Triumph of the aggregate

It is easy to misinterpret the application of aggregate data to individuals by equating group probabilities to individuals [16]. Thus, if a trial of excisional surgery for melanoma showed that 95% of participants (similar to your patient) were clear of the disease after 5 years, one cannot then tell the patient “You have a 95% chance of being clear at 5 years with this treatment,” since this 95% refers to the group and not the individual. The patient in front of you will either clear or not clear – the patient’s fate or response is already determined at that moment by that patient’s microdisease and other cofactors such as immunological status, much of which may be under genetic influence. However, it is correct to tell that patient that “95% of people similar to you are clear at 5 years.”

This inability to directly apply aggregate data directly to individuals is not unique to RCTs; it applies to most basic science [17]. Everyday “clinical experience” with a particular drug is, after all, a form of aggregation of data based on recollection of treatment responses amongst *groups* of previous patients. The same difficulties in predicting whether the next patient will respond to that drug, and by how much, exist more in anecdote-based clinical practice than in an evidence-based practice approach.

Thus, it is important to consider a number of factors when thinking about study participants and the individual patient [4]. There may be pathophysiological differences that could lead to a diminished treatment response. For example, people with atopic eczema may not respond well to reduction of house dust mites if they were not allergic to house dust mite in the first place. There may be important social and economic differences that may diminish treatment compliance, and hence response. For example, a single parent with four children and a full-time job may not have the time to diligently apply short-contact dithranol (anthralin) to their widespread plaque psoriasis every day. Comorbidities such as renal disease might also affect the treatment response, either directly by affecting drug metabolism and clearance or indirectly through drug interaction and compliance. Sometimes, the patient’s baseline extent of disease profoundly affects the effectiveness of the treatment being contemplated, in that those with little disease to begin with have little to gain. Patients with low potential to benefit from treatment also may still be at a high risk of adverse effects, thus resulting in a narrower risk/benefit ratio than those with severe disease [18].

### Do the outcomes make sense to me?

Even though you might have specified which outcomes are important in your structured evidence-based question – for example, “the proportion of patients cleared at 6 months” – very often the studies will contain a number of other short-term outcomes [19]. You then have to decide whether these outcomes provide useful clinical information. In most circumstances, there will be at least some information that makes some clinical sense to you.

### Take care in interpreting composite scales

Particular care should be taken in interpreting quantitative scales. Scales that combine several objective clinical signs and symptoms into an overall score are commonly used in dermatology RCTs. Despite their appearance of objectivity, most of them have rarely been tested for validity [20,21]. More importantly, such composite scales are often difficult to translate into clinical practice. What, for instance, does a difference of eight units ( $P < 0.05$ ) as the mean change in the psoriasis area and severity index (PASI) score from baseline between two treatments mean to you? Or when comparing methotrexate versus azathioprine for atopic dermatitis in atopic eczema, does a difference of 8.7 points using the SCORAD scale really mean that the two treatments can be considered equivalent [22]? Such scales are typically not linear (i.e., a patient with a PASI score of 30 is not “twice as bad” as a patient with a score of 15). A lot of psoriasis over the covered areas of the body does not mean more distress than a little bit of psoriasis on the backs of the hands and face.

### Sensitive scales amplify effects

Scales that are very sensitive to change amplify statistically significant changes that may be clinically unimportant. Take, for example, the trial of 2% minoxidil against placebo for androgenetic alopecia in women [23]. This study found a statistically significant increase in non-vellus target area hairs in the minoxidil-treated group in comparison with the vehicle-treated group after 32 weeks ( $P = 0.006$ ), although the “subjects discerned no difference.” The study, which was otherwise well conducted, should have concluded “something seems to be happening, but it is not clinically useful.” However, the authors’ conclusion was that “Two percent minoxidil appears to be effective in the treatment of female androgenetic alopecia.” Effective for whom?

### Too many scales and too many short-term studies

Given the profusion of scales used in dermatology (there are at least 21 named and at least 30 unnamed scales in atopic eczema alone) [21,24], it is quite easy to introduce bias by choosing a scale containing features that will enhance one’s own product in comparison with competing products. Introduction of a new scale is another potential source of bias, since they can increase the likelihood of showing a treatment benefit [25]. Lack of suitable long-term outcomes is another problem frequently encountered in dermatology clinical trials. For example, atopic eczema is a long-term condition for most sufferers, yet of the 272 RCTs summarized in a previous systematic review, most have been less than 6 weeks in duration [19]. Other factors, such as the frequency and duration of the remission, are key components in assessing the value of therapy. It is therefore important when reading a trial report to think of the time frame for outcomes as well as the type of outcome.

One significant advance in relation to outcome measures is the concept of development of core outcome sets. Core outcome sets simply refer to a small number (typically three or four) outcomes that should always be measured in clinical trials of a particular disease – usually a patient-reported outcome, an objective measure of clinical signs and a quality of life and adverse effect measure. The development of core outcome sets allows readers of published trials to make comparisons of trials that are conducted across the world as well as making it easier for them to be included in a meta-analysis within a systematic review. The Harmonizing Outcome Measures for Atopic Eczema (HOME) project is an example of an international group developing core outcome



domains and instruments for measuring those domains in atopic eczema/dermatitis [26], and links to similar initiatives in dermatology can be found from their website (<http://www.homeforeczema.org/>) or the COMET (Core Outcome Measures in Effectiveness Trials) initiative website (<http://www.comet-initiative.org/>).

### Look for outcomes that are clinically important

Although composite scales may be useful in the early development of a drug, in that they may show that something is happening, the key question within the framework of pursuing an evidence-based prescription is whether something *useful* is happening. Given the limitations of quantitative composite scales in dermatology, what should one look for in terms of outcomes that can best inform practice? In the absence of established core outcome sets, see what the patients who participated in the trials thought of their treatment, using simple measures such as the proportion of participants with a “good or excellent” response or simple categorical measures such as percentage cleared. Did the patients’ quality of life improve? Although such measures are subjective, reduction in distress is the precise treatment goal for many chronic skin diseases? Patient center outcomes help generalize the meaning of treatment responses across cultures, since some cultural groups may voice their complaints more or less than others.

Objective measures are, of course, also needed, especially when interventions are not blinded. Objective measures are also more useful in some diseases (for example, to assess the histological clearance of treatments for basal cell carcinoma). Again, the objective outcomes need to be simple enough for most physicians and their patients to understand (for example, the proportion of recurrences within 5 years, rather than hazard ratios for first recurrence).

## Magnitude of treatment effects

### How big?

Even if a trial yields a result that is clinically meaningful, it is important to ask, “Is the *size* of that benefit likely to be helpful for *my patient*?” Even when the study benefits are of large magnitude, they may still not be enough. Consider a patient with a facial port-wine stain who is treated with pulsed tunable dye laser, and who achieves a 70% reduction in the total surface area involved. We might be impressed by such a magnitude of gain, but if the patient is still unhappy because they feel that the stigma associated with the residual lesion is just as disabling, or that the odd pattern of circular pale holes left by the laser within the lesion draws even more attention to it, then this is a treatment failure.

Thus, it is crucial to consider not only whether a treatment is effective in a published report, but also *how* effective it is. Large studies tend to find small but possibly clinically irrelevant benefits, and large benefits reported in first reports tend to be reduced or contradicted in subsequent studies [27]. It follows that an important part of the discussion with the patient is to agree on what is possible or not possible in terms of realistic treatment objectives.

### Number needed to treat

Because many interventions in medicine are of only modest effect, their apparent benefit may not be that noticeable after one has tried the intervention on a few patients. One way to understand the magnitude of benefit in relation to baseline risk is to use the concept of “number needed to treat” (NNT) [28]. NNT refers to the number of patients that you would need to treat in order to see one addi-

tional success in the new treatment in comparison with another treatment. NNT is calculated simply as the reciprocal of the difference in success rates between the treatments being compared. Thus, a new treatment that results in clearing of psoriasis in 40% of patients, compared with 30% for the conventional treatment, translates into a risk difference of 10% (40% – 30%) and an NNT of 10 (1/0.10). In other words, one needs to treat 10 patients to clear one additional patient.

Patients’ and physicians’ views regarding the threshold for what might constitute a useful NNT may differ significantly. Thus, in a study of perspectives of physicians and patients on anticoagulation for atrial fibrillation, patients placed significantly more value on the avoidance of bleeding than did doctors [29]. Again, the message here is not to think of NNT as belonging exclusively to doctors – patients also need to be incorporated into the decision-making process in determining what is useful and important.

It is also important that the dermatologist and patient decide for themselves what might constitute a useful NNT, rather than accepting the conventions that have been derived from acute medicine. For example, it may be perfectly justifiable to treat 200 patients with low-dose aspirin in order to prevent one stroke. It would certainly not be justifiable to treat 200 patients with a new antibiotic to gain one extra short-term remission of acne. In a pressurized health service, the value of a new treatment for plaque psoriasis with an NNT of 20 might be questionable. Perhaps the opportunity costs associated with seeing and treating the extra 20 patients needed in order to achieve one extra response from the new treatment could be better spent discussing other treatment options with them, or assessing other new patients. Despite these caveats, the NNT is a more useful tool than relative risk or odds ratios for translating the evidence back to the patient. The concept of NNT may also be applied to adverse effects where it is known as the number needed to harm. A detailed review of NNT in dermatology may be found elsewhere [30].

## Adverse events

### Trials are not a useful source of rare but serious side effects

As highlighted in Chapter 10, adverse events are often overshadowed by an emphasis on the positive treatment benefits in clinical trials. Details of reasons for withdrawals are frequently missing from trial reports altogether, and failure to perform an intention-to-treat analysis may compound this omission, as dropouts may be related to lack of efficacy or to adverse events that are not obviously related to the trial medication [31]. Rare but important side effects such as minocycline pigmentation are unlikely to show up in small clinical trials and often emerge as subsequent case reports or during postmarketing surveillance. Simply stating that no serious liver problems occurred in 100 patients taking traditional Chinese herbs for atopic eczema is still compatible with an upper 95% confidence limit of 3% if a larger population were tested [32].

Particular efforts should therefore be made to scrutinize trials for a list of the frequency and severity of adverse events, as discussed in Chapter 10. As the events surrounding the thalidomide tragedy remind us, caution should be exercised when using new treatments that have not been tested on thousands of patients. Additional literature sources and postmarketing surveillance studies need to be scrutinized before one can reassure patients on side-effect issues with a reasonable degree of certainty.

## Limitations of aggregate data

Just as for assessing treatment benefits, aggregate data on side effects can be misleading. Thus, when comparing two types of corticosteroid, one may find that the mean decrease in skin thickness is similar in the two groups. However, if further scrutiny of the individual data shows that two children in one group developed skin thinning with noticeable visible striae, then that observation might influence your decision not to use such a treatment, despite the relative reassurance provided by the group means.

## Communicating risks

How to communicate risk presents its own problems, with different conclusions being reached by doctors and their patients, depending on how the information is presented in terms of relative or absolute risk [33]. Paling and others suggest that supplementing verbal data with numerical data is key [34,35]. Absolute numbers, rather than relative or percentage changes, should be used, and the same denominator should be used to compare with other risks in order to provide context. Risk should be communicated in straightforward numbers that are easily understood, such as 1 in 1000, and the figures should relate to a specific time period – for example, per year or lifetime. Visual aids, such as those depicting what can happen amongst a group of a thousand people undergoing an intervention (the Paling Palettes, <http://www.riskcomm.com/palettes.php>), can be especially helpful [34].

Even when the risks are understood, weighing up the pros and cons of an intervention is a highly variable affair. It depends on the type of information presented to the patient, and the manner in which the information is presented. Thus, a doctor who believes that a patient with psoriasis needs ciclosporin may play down the possibility of permanent kidney damage by their body language and by saying that they have treated hundreds of patients without any problem. However, for another patient who has requested the same treatment, but for whom the doctor considers ciclosporin inappropriate, he or she may use the very same potential adverse event as a “threat” to dissuade the patient.

## Decision-aid approaches to weighing up risks and benefits

Combining the values of treatment benefits versus risks for individual patients has been tackled using approaches such as decision analysis – a process in which the sequential choices faced by patients are made explicit [24,36]. Patients are then invited to place their own values on the various potential gains and losses. These decision-aid methods have been used extensively in areas such as amniocentesis for detecting fetal abnormalities, but less so in dermatology [25,37,38]. Simplifications of a decision-analysis approach, such as the likelihood of being helped or harmed, have been advocated by others [26,39].

## What are the patient’s values?

### Values and belief models

Even if the external evidence suggests a good treatment for your patient, they might have a number of reasons for choosing or not choosing that treatment. For example, a teenager who consults you with acne, whose friend developed hepatitis whilst taking oxytetracycline, might initially refuse that treatment option. If that drug is really the best choice, the dermatologist can explain how rare such an event is and reach a joint decision with the patient. Another

patient with acne might come demanding treatment with isotretinoin simply because their friend at school had similar treatment with excellent long-term results and tolerable side effects. Although such a declaration might influence the consultation, it does not automatically mean that the dermatologist will concede to such a request if they feel that the treatment is not in the patient’s best interest (for example, very mild disease or a history of several unplanned pregnancies). Application of the best external evidence requires a dialogue with the patient in order to explore their values and expectations.

Patients sometimes prefer to use something that they perceive to be more “natural” – for example, evening primrose oil rather than synthetic topical corticosteroids for atopic eczema. Sometimes patients prefer to forgo pharmacological treatment and instead undertake various measures to manipulate their environment. Others just prefer to take a few pills and forget about it. Some like creams, others like ointments. Some people do not wish to be involved in lengthy discussions of treatment options if indeed they believe that their doctor is the best person to help them choose a treatment option. For example, a person with a basal cell carcinoma may be happy to be recommended surgical excision rather than debate the 10 or so treatment options available to treat such lesions.

Issues of personal perception, belief models, locus of control, and personal experience should all contribute to the richness of a consultation with a patient. Although patients’ treatment choices may at times appear to be at odds with the external trial reports, patients are human beings who have their own sets of preferences and values, and these preferences need to be respected and understood [40].

## And if the treatment still does not work?

After agreeing on a treatment, a patient may return saying that the treatment does not work. After obvious issues have been explored, such as compliance and whether adverse events can be avoided (e.g., the presumed “allergic reaction” from topical benzoyl peroxide may be a predictable irritant reaction that could be circumvented by less frequent or vigorous application), other treatment options are often discussed. If several treatments fail in a particular patient, the patient may belong to a subset with refractory disease, making it even more difficult to generalize from clinical trials of people with more responsive forms of the disease. Dermatologists frequently face the problem of trying several drugs in succession. External trial evidence could be improved by better descriptions of study participants in terms of previous treatments, and by means of sequential RCTs that try different treatment approaches following failure of a treatment.

## Conclusions

Applying evidence back to the patient is often the most difficult and neglected step in the practice of evidence-based dermatology. The question of how best to relate universal evidence to the particular has always been a doctor’s dilemma. Clinical judgment is at the heart of this process [28,41], and requires consideration of several factors, including an appraisal of the magnitude and meaning of the treatment benefit and adverse events in relation to the patient’s values and preferences. Presenting the evidence back to the patient is a complex process requiring good communication skills and an appreciation of the limitations of the generalizability of trial data in terms of trial participants, relevance, and trade-off between benefits and harms.

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# PART III

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## The evidence

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## SECTION 1 Common inflammatory skin diseases

Luigi Naldi, editor

### CHAPTER 19

## Acne vulgaris

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### Background

#### Definition

Acne vulgaris is a pervasive disease of the pilosebaceous follicles of the skin, which are located on the face, back, and chest. The disease has a range of clinical expression and can be classified according to the predominant lesion type:

- Noninflammatory or comedonal acne is primarily composed of open comedones (blackheads) and closed comedones (whiteheads), with little or no inflammatory involvement.
- Inflammatory acne is characterized by inflamed lesions (ILs: pustules, papules, and nodules) and can be further subdivided into papulopustular, nodular, and conglobate, depending on the predominant lesion type.
- Conglobate or nodulocystic acne is characterized by ILs that have progressed to form abscesses or granulomas [1]. Acne fulminans is a severe form of conglobate acne.

#### Incidence/prevalence

Estimates of overall prevalence vary considerably and depend on the study populations and epidemiological methodology used. The disease is defined by a continuum of severity (Figure 19.1), along which members of the adolescent population are placed; it is estimated that up to 30% of teenagers have acne of sufficient severity to warrant medical treatment [1]. An increasing number of women in their twenties develop late-onset acne, and surveys of adults over the age of 25 years have reported prevalence of 22% in males and 40% in females [2,3].

#### Etiology/risk factors

Acne results from pathological changes in the pilosebaceous duct (PSD). Thickening of the follicular stratum corneum (hypercornification) leads to blockage and accumulation of sebum, which is produced in large quantities in response to the androgen surges that accompany puberty. The resident skin commensal bacterium, *Propionibacterium acnes*, proliferates in the lipid-rich sebaceous follicles, causing accumulation of bacterial metabolites, sebum, and dead cellular material. Follicular occlusion blocks discharge, and an inflammatory response ensues. The extent and duration of the inflammation, and hence the severity of the acne, may be determined by individual variation in the immune response to *P. acnes*.

The onset of acne is associated with adrenarche, although androgen markers and mild comedonal acne have been detected in children under 10 years of age [4,5], particularly in girls who have an earlier onset of puberty [6]. Although the overall incidence is roughly equal in both sexes, with the peak rates occurring at 17 years of age [7], boys tend to have more severe disease [8]. There is no evidence that ethnic or racial differences influence the development of acne, although blacks have a higher incidence of disease [9]. Whilst genetic factors are also thought to influence susceptibility to acne [10,11], the mode of inheritance has not been determined.

#### Prognosis

Most cases of adolescent acne clear spontaneously over time. There are, however, two common forms of postadolescent acne: persistent acne commences in adolescence, but does not resolve and is generally resistant to antibiotic therapy, and late-onset acne is generally less severe, evolves more commonly in women after 25 years of age, and has been linked to abnormalities in plasma androgens [11,12].

The total burden of acne extends beyond financial costs; the impact on the individual can be devastating, as the disease occurs at an age when its effects are acutely felt. The cosmetic changes associated with acne have been linked to anxiety, depression, social isolation, and interpersonal difficulties [13].

#### Aims of treatment

Treatment aims to alleviate symptoms and accelerate healing of lesions in the short term, and in the longer term to limit disease activity, scarring, and the impact of the disease on quality of life.

Treatment options are commonly classified according to route of delivery and mode of action. The comparative data on various therapies are limited, and individual trials have obtained contradictory results, largely because of inadequate trial design and unfair comparisons in terms of dosage. Isotretinoin is the only acne treatment that can induce persistent remission. All other acne treatments are palliative, and whilst improvement of symptoms and control of disease progression is possible, prolonged therapy is needed.

#### Relevant outcomes

Disease severity is assessed by a visual assessment of the number of lesions and extent of disease. Although numerous visual assessment



Figure 19.1 Mild to moderate acne.

methods of varying complexity exist, at the basic level they can be subdivided into grades or counts. In both cases, there are three levels at which assessment can be made:

- 1 an overall or “global” evaluation;
- 2 subdivision according to the predominant morphological component (i.e., inflammatory or noninflammatory);
- 3 separate evaluations of individual lesion type (e.g., comedones, papules, and pustules).

The results are generally expressed as an absolute or percentage change from the onset of therapy and are commonly transformed to give the numbers of individuals attaining a given level of improvement; for example, 50%.

Other important outcomes include changes in quality of life, scarring, patient satisfaction, tolerability and adverse events, speed of action, and treatment-free interval.

### Search methods

In the previous edition of this book, this chapter used a systematic review prepared for the Agency for Healthcare Research and Quality (AHRQ) [14] as the primary source of evidence, supplemented by evidence located by searches in the following databases: Cochrane Library (issue 1, 2002), Cochrane Skin Group Specialist Trial Register, Medline (1966 to February 2002), and Embase (1980 to February 2002). The updated chapter includes searches of each of these databases from 2002 to February 2012 for systematic reviews and randomized controlled trials (RCTs).

### Questions

#### Is there any evidence to support the routine use of skin cleansers and/or abrasives in the management of mild to moderate acne?

The impact of detergent bases on the control of sebum has not been ascertained, although it has been hypothesized that removal of

sebum may enhance the activity of topically applied antibacterials. There is also controversy as to whether exfoliation using abrasives clears blocked PSDs and speeds up lesion healing, or whether associated irritancy and drying may aggravate inflamed skin. Antibacterial agents reduce surface bacteria, but there is little evidence to suggest that they penetrate the PSD.

### Efficacy

The AHRQ review included four relevant RCTs [15–17], and additional searches provided four individual trials and a review that included two RCTs [18–22]. Five of the studies were double-blinded (Table 19.1); only two studies enrolled more than 100 patients.

The largest RCT showed that an acidic soap-free syndet was less of an irritant than soap and reduced both ILs and noninflammatory lesions (NILs) in 120 patients with mild acne who were not taking any other anti-acne medication [16]. There were no significant differences between the groups, although the individuals using soap experienced a mean increase in both NILs and ILs over 12 weeks and 23 of 57 experienced irritation, compared with one of 57 in the soap-free group. Similar results were also obtained in more recent studies [21]. A double-blind RCT included 50 patients with moderate acne currently using topical Benzamycin (benzoyl peroxide) or Benzamycin plus adapalene [23]. After 4 weeks of additional treatment with soap or a mild syndet bar, patients using soap had more peeling, dryness, and irritation, whereas those using syndet soap had no significant changes in skin irritation. The mild cleanser was more effective in reducing the severity scores of negative characteristics such as acne, itching, and oiliness. A recent RCT included 13 patients with mild acne [24]. After 8 weeks of treatment with a mild cleanser, patients had a significant decrease in both NILs and ILs. Patients treated with the cleanser plus triclosan, salicylic acid, and azelaic acid, however, showed a significantly larger decrease in ILs both clinically and histologically compared with cleanser alone. These results demonstrate the compatibility between mild cleansers and these various treatment options.

Cleansers containing the antibacterial hexachlorophene produced improvement in equivalent numbers of patients to triclosan in a 12-week crossover trial with 34 patients [15], although no wash-out period was permitted. Eleven patients experienced local reactions to triclosan and nine to hexachlorophene; hexachlorophene is now not recommended. Chlorhexidine was shown to produce equivalent significant reductions in NILs and ILs in 50 patients with moderate acne in comparison with 5% benzoyl peroxide at 12 weeks. It also produced significantly greater reductions in ILs and NILs than in those treated with the vehicle alone in 110 individuals, again at 12 weeks [20]. Chloroxylenol 0.5% in combination with 2% salicylic acid was as effective as 5% benzoyl peroxide in reducing NILs and ILs in 37 patients with mild to moderate acne when applied to the face twice a day [22]. Patients in the combination group experienced significantly less erythema and photosensitivity than those using benzoyl peroxide.

In individuals treated with tetracycline, 500 mg twice daily, additional use of antibacterial soap in a 4-week period offered no benefit over the use of normal soap. However, it was shown to significantly reduce the incidence of acne flare in responders to 4-week tetracycline therapy in a 90-day follow-up (13/30 flared vs 22/31) [19].

After 12–14 weeks in a double-blind RCT, povidone-iodine skin cleanser led to improvement in nine of 10 patients with mild acne, compared with three of seven in the vehicle group. The results are invalidated, however, by the high losses to follow-up [17]. The results in a second group of patients with more severe acne who

**Table 19.1** RCTs of skin cleansers and abrasives.

First author, ref.	Comparators	Patients (n)	Severity	Duration (weeks)	Blinding	Results	Comments
Bettley (1976) [15]	1. Hexachlorophene 2. Triclosan	34	1/2/3	6/6	0	No significant differences; drug improved: 21/28 vs 22/28; local reaction: 11 vs 9	6 LTF; not ITT; crossover study; no wash-out period
Fulghum (1982) [18]	1. Sulfur/salicylic acid cleanser with polyethylene granules 2. Sulfur/salicylic acid cleanser	53	1/2	8	0	Both reduced ILs and NILs; no significant differences; equal sensitivity	7 LTF; not ITT; split half-face study; no concomitant therapy
Kanof (1971, part 2) [19]	1. Antibacterial soap 2. Soap	51	3	>12	A, P	Flare 13/30 vs 22/31	Tetracycline responders; no details on concomitant therapy
Kanof (1971, Part 1) [19]	1. Antibacterial soap 2. Soap	86	3	4	A, P	Response 30/44 vs 31/42	All tetracycline 250 mg 2 or 3 times daily; no details on concomitant therapy; not ITT
Korting (1995) [16]	1. Acidic syndet bar 2. Soap	120	1	12	0	1 reduced ILs and NILs; 2 increased ILs and NILs; no intergroup comparison	2-week wash-out; 6 LTF; ITT analysis; soap 5 dropouts exacerbation; no concomitant therapy
Milikan (1976, A) [17]	1. Povidone-iodine cleanser 2. Vehicle	30	1	12–16	A, P	Improved 9/10 vs 3/7; intolerance 1 = 2	13 LTF; not ITT
Milikan (1976, B) [17]	1. Povidone-iodine cleanser 2. Vehicle	30	2	12–16	A, P	10/13 vs 12/14 improved; 0 intolerance	3 LTF; all tetracycline 250 mg 1 or 2 times daily
Stoughton (1987, A) [20]	1. Chlorhexidine gluconate cleanser 4% 2. Benzoyl peroxide 5%	50	2	12	A	No significant differences in ILs or NILs	3 LTF; not ITT; no concomitant therapy; twice-daily application
Stoughton (1987, B) [20]	1. Chlorhexidine gluconate cleanser 1.4% 2. Vehicle	110	2	12	A	1 = 2 ILs and NILs; dry skin: 3 vs 1	17 LTF; not ITT; no concomitant therapy; twice-daily application
Millikan (1981) [25]	1. Buf-Puf 2. No abrasion	50	2	12	A	No intergroup comparisons; suggestion that abrasion better, but no data	2 LTF; not ITT; all patients received 5% benzoyl peroxide; split-face study
Subramanyan (2004) [21]	1. Benzamycin with or without Differin + soap 2. Benzamycin with or without Differin + syndet bar	50	2	4	A, P	Patients in soap group had increased rates of peeling, dryness Reduced scores for syndet group in itching, acne, and oiliness	
Subramanyan (2003) [23]	1. Current medications + mild cleansing lotion (Dove) 2. Current medications	25	1	4	A, P	Significant reductions in NILs, ILs, erythema, dryness	
Boutli (2003) [22]	1. Chloroxylenol 0.5% + salicylic acid 2% cream 2. BP 5% gel	37	1/2	12	A, P	At week 12, both groups significant in ILs and NILs (60% and 54% for BP group and 56% and 56% for chloroxylenol + salicylic acid group)	Chloroxylenol + salicylic acid slightly stronger keratolytic activity. No difference in reduction of papules. Erythema and photosensitivity significantly lower in chloroxylenol + salicylic acid group

Severity: 1, mild; 2, moderate; 3, severe. Blinding: 0, open; A, assessor; P, patient. BP, benzoyl peroxide; LTF, lost to follow-up; ITT, intention-to-treat; ILs, inflamed lesions; NILs, noninflammatory lesions.

also received tetracycline, 250 mg once or twice daily, were equivocal (10/13 compared with 12/14) [17]. Only one case of mild itching was experienced.

The addition of abrasives to a combination of sulfur and salicylic acid in a split-half-face study in 44 patients did not show any difference in either efficacy or tolerability after 8 weeks. The potential for the effects of the active ingredients to mask all other effects must be considered [18]. One split-face study evaluated the use of addi-

tional abrasion to 5% benzoyl peroxide therapy, but there were no intergroup comparisons to validate the authors' claim that the side of the face treated with abrasion showed better results [25].

### Adverse effects

Soaps are of alkaline pH and are known irritants, causing itching, dryness, and redness; acidic soap-free cleansers may therefore be preferable. Aggressive use of abrasives may irritate skin, and for that

reason common sense suggests that they should not be used in conjunction with topical agents such as benzoyl peroxide, which sensitize the skin, unless tolerance has initially been demonstrated. Dermatological reactions are idiosyncratic and cannot be predicted, and the patient should be advised to discontinue use immediately if irritation develops. Like any topical agent, it is possible that antibacterial cleansers and abrasives are less suitable in individuals with sensitive skin. The literature does not support a link between the use of topical antimicrobials and the emergence of antibiotic resistance [26].

### Comment

The number of propionibacteria on the skin surface is increased by soap and decreased by synthetic detergents [27]. This may be due to the changes in skin pH, which is increased by soap [27]. There is no evidence either for or against the use of abrasive agents, either alone or in combination with topical treatments. There is evidence to suggest that antibacterial skin cleansers may be effective in the management of mild acne [17], and may produce similar outcomes to benzoyl peroxide in moderate acne [20]. However, the long-term benefits of “step-up” management strategies versus aggressive therapy from onset have not been examined. In addition, recent evidence suggests a rebound effect in ILs after discontinuation of cleanser monotherapy [24]. There is no evidence that antibacterial cleansers offer additional benefits when used in conjunction with oral antibiotics in individuals with more severe acne, but they may help maintain improvement following the termination of antibiotic therapy [19]. The impact of increased contact time during washing has not been examined.

### Implications for clinical practice

In individuals with mild acne whose disease is not adversely affecting their quality of life, antibacterial washes should be considered in the choice of first-line management strategies in step-up approaches. They should also be considered in the maintenance of patients who have ceased therapy following response. They should not be prescribed routinely in patients who are receiving more aggressive therapy, as there is no evidence of any additional benefit. Syndet bars may be preferable to soap in skin care routines.

### What is the role of topical nonantibiotic agents in the treatment of mild primarily noninflammatory acne?

Mild acne consisting of open and closed comedones with a few ILs is commonly treated with topical agents. A number of options have been effective in placebo-controlled RCTs, and all can be used either alone or in combination. Options include the topical retinoids (isotretinoin, tretinoin, adapalene, and tazarotene), benzoyl peroxide, salicylic acid, and azelaic acid.

### Topical retinoids

Topical retinoids reduce abnormal growth and development of keratinocytes within the PSD. This inhibits microcomedo formation and therefore subsequently reduces the number of comedones and ILs.

### Efficacy

Evidence for the efficacy of topical retinoids was available from two systematic reviews [14,28], which examined 20 RCTs and split-face studies [29–47]. Fourteen further studies were located through searching [48,49] (Web Table 19.1). Focusing only on comparisons

that had at least two RCTs of acceptable quality showing moderate to strong statistical evidence, the authors of the AHRQ review concluded that 0.1% adapalene and 0.025% tretinoin were equally efficacious and that motretinide and tretinoin were equally effective. The second review [28] evaluated five RCTs of 0.1% adapalene gel versus 0.025% tretinoin [33–35,38,50]. All RCTs were investigator-blind, and a total of 900 individuals with mild to moderate acne were enrolled. Using data collected from intention-to-treat (ITT) analyses, equivalent efficacy against total lesion counts was demonstrated, with adapalene showing greater activity at 1 week.

Of the RCTs that presented data [33,34,37,38,50–54], mean percentage reductions in NILs ranged from 36% to 88% in the 0.1% adapalene group, from 33% to 83% in the 0.025% tretinoin group, and 50% to 86.9% in the 0.05% tretinoin and isotretinoin groups at 12 weeks. Percentage reductions in ILs were 35–69% and 38–71%, respectively. Higher strength adapalene (0.5%) was investigated in one 25-patient split-face study and was shown to have greater activity than 0.1% adapalene against both ILs and NILs, but was associated with more erythema [49]. Two strengths of adapalene (0.1% and 0.03%) were evaluated in five studies enrolling a total of 1053 patients with mild to severe acne [32,33,53–55]. The higher strength produced greater reductions in IL and NIL counts, but was associated with more irritation in some studies, whereas others showed similar rates of erythema.

Topical tazarotene is more effective than other topical retinoids, including adapalene and tretinoin, in the treatment of mild to moderate acne. An RCT compared daily-use tazarotene 0.1% gel with daily 0.1% tretinoin in 169 patients. Tazarotene was more cost effective and was associated with greater reduction of NILs [56]. Both regimens were well tolerated. A meta-analysis of data from multicenter, double-blind RCTs included data on 688 patients who used tazarotene 0.1% gel or cream once daily for 12 weeks. Tazarotene was effective and well tolerated, regardless of the patients' acne severity, skin type, sex, or ethnicity [57]. Another study compared tazarotene monotherapy with three tazarotene combination therapies and clindamycin monotherapy in 440 patients with mild to moderate acne. Tazarotene alone was as effective in reducing NILs as tazarotene in combination with the erythromycin–benzoyl peroxide combination and clindamycin [58]. All tazarotene-containing regimens were more effective than clindamycin alone. For ILs, tazarotene plus erythromycin–benzoyl peroxide combination therapy was significantly more effective than all other treatments.

Recent RCTs show noninferior efficacy of adapalene compared with tazarotene. In an RCT with 160 patients suffering from mild to moderate acne, adapalene 0.3% gel demonstrated similar efficacy in reduction of NILs and ILs compared with tazarotene 0.1% gel. In addition, the adapalene 0.3% gel caused less erythema, scaling, dryness, and stinging/burning [59]. Similar results were demonstrated in an RCT comparing adapalene 0.1% gel with tazarotene 0.1% cream [60]. Another RCT also showed adapalene 0.1% monotherapy equal to “switch therapy” (6 weeks of adapalene 0.1% gel plus 6 weeks of tazarotene 0.1% cream) in a 12-week RCT of 100 subjects with mild to moderate acne, though the study may have been underpowered to evaluate efficacy [61]. Few comparative data for retinoids against other agents were found. In 77 patients with mild to moderate acne, 0.05% isotretinoin applied twice daily was slightly less effective than 5% benzoyl peroxide against ILs and NILs and was slower to resolve ILs [46]. The results for tretinoin against benzoyl peroxide [62–64] were equivocal, and there were no differences in the rate of adverse events. A recent open-label



RCT compared 0.1% adapalene with 4% benzoyl peroxide using percentage clearance as the primary outcome [65]. Both therapies demonstrated similar efficacy, with 78% and 76% of patients showing excellent clearance (60–80% reduction in lesions) in the adapalene and benzoyl peroxide arms, respectively.

### **Adverse effects**

Topical retinoids induce local reactions and should be discontinued if the reaction is severe. All studies presenting data suggested that 0.1% adapalene causes less local irritation than 0.025% tretinoin [49] and that the rate of local reactions with both agents increases with concentration [32,33,49,55,66]. Recent RCTs demonstrated that newer delivery systems of potent topical retinoids, such as tretinoin and isotretinoin, can provide a better tolerability profile than adapalene [67]. Retinoids increase the sensitivity of skin to ultraviolet light and should, therefore, be applied at night and washed off in the morning. Rarely, eye irritation, edema, and blistering of the skin occur, and hypopigmentation may result from tretinoin use.

### **Comment**

There remains uncertainty as to whether retinoids applied topically cause birth defects, and whilst minimal absorption has been demonstrated following topical application [68], as a precaution retinoids should not be used during pregnancy or by women planning pregnancy. Lastly, one large RCT designed to evaluate the efficacy of topical tretinoin for actinic keratoses in an older male population was stopped prematurely due to increased all-cause mortality in the treatment group. Although extensive analysis failed to yield a mechanism for this result other than chance, these results should be discussed with older men using or considering the use of tretinoin [69].

### **Implications for practice**

The comedolytic action of topical retinoids suggests that they should be used in the treatment of mild acne. However, as this activity halts subsequent lesion formation, they are also suitable for moderate to severe acne and can be used in conjunction with topical and oral antibiotics. Benzoyl peroxide inactivates tretinoin, so the two agents should not be applied simultaneously; if used in combination, one should be applied in the morning and one at night. All topical retinoids cause local sensitivity reactions, which are less common with adapalene. To limit local sensitivity, topical retinoid therapy should start at a lower strength, be applied every third night, and increase gradually.

### **Benzoyl peroxide**

The lipid solubility of benzoyl peroxide allows it to penetrate the PSD. It has comedolytic, anti-inflammatory, and bactericidal activity and is therefore suitable for management of individuals with mild inflammatory or mixed acne. It can be bought over the counter from pharmacies and is available in a number of formulations, in strengths of 2.5–10.0%.

### **Efficacy**

The AHRQ systematic review [14] examined seven placebo-controlled RCTs in patients with mild to severe acne [46,70–75] (Web Table 19.2). Changes in both NILs and ILs were consistently significantly superior in the active group. Two RCTs reported mean reductions in lesion counts with 5% benzoyl peroxide: 52% and 60% for ILs and 30% and 52% for NILs [46,72]. The reductions in

the vehicle comparator arms were less than 10% in each case. Four RCTs compared different dosages of benzoyl peroxide [62,70,76], and no evidence was found to support a dose–response effect (Table 19.2).

Three RCTs compared topical tretinoin with 5% benzoyl peroxide [63,64,77]. Tretinoin was more effective against NILs up to 12 weeks, but benzoyl peroxide had a greater impact on ILs. Another trial compared 2.5% benzoyl peroxide, 0.1% adapalene, 0.1% adapalene/benzoyl peroxide combination, and vehicle [78]. Combination therapy was significantly more efficacious in reducing total lesions than any other tested treatment, showing a 62.1% reduction in ILs and a 53.8% reduction in NILs at 12 weeks. Benzoyl peroxide monotherapy ranked second efficacious with a 50% reduction in ILs and a 49.1% reduction in NILs.

A recent split-face RCT compared solubilized 5% benzoyl peroxide gel to 5% benzoyl peroxide/1% clindamycin in 23 patients with moderate acne [79]. With 4 weeks of therapy, patients demonstrated a mean reduction of 42% and 28% of NILs in the solubilized benzoyl peroxide arm and the benzoyl peroxide/clindamycin arm, respectively. In addition, there was a 70% reduction in ILs with solubilized benzoyl peroxide and a 61% reduction in ILs with benzoyl peroxide/clindamycin. Studies also show that 5% benzoyl peroxide has similar efficacy to 20% azelaic acid in mild acne [80].

A recent meta-analysis of 23 RCTs including 7309 patients compared benzoyl peroxide in combination with salicylic acid or clindamycin with benzoyl peroxide and clindamycin monotherapy. Benzoyl peroxide plus salicylic acid proved most efficacious in the reduction of NILs and ILs at early time points (2–4 weeks). Benzoyl peroxide plus salicylic acid and benzoyl peroxide plus clindamycin demonstrated similar results at later time points (10–12 weeks). Though large, the study is of moderate clinical use owing to possible selection bias and the lack of patient-oriented outcomes. In addition, it is questionable how much combination therapy improves efficacy over monotherapy [81].

### **Adverse effects**

Benzoyl peroxide is commonly associated with local irritation that presents as erythema, peeling, dryness, burning, stinging, itching, and soreness. Use of an emollient or water-based gel may reduce these reactions. Recent RCTs also demonstrate that new benzoyl peroxide delivery systems, such as combination products with urea as well as microparticle benzoyl peroxide, minimize noxious side effects while maintaining efficacy [82]. However, these new preparations have not been rigorously evaluated [83]. Allergic contact dermatitis, characterized by erythema, small papules, and pruritus, may occur rarely. RCT evidence shows that the side-effect profile of a 2.5% preparation is similar to that of 5% [70,76] and less than 10% preparations [70]. Combinations of benzoyl peroxide with antibiotics are unstable because of degradation of the antibiotic by benzoyl peroxide. Benzoyl peroxide will bleach hair and fabrics, and patients should therefore be counseled accordingly. It is safe for use during pregnancy. There were concerns that benzoyl peroxide might promote skin cancer [84,85], but these have been refuted [86].

### **Comment**

A major concern with the continued use of antibiotics, topical and oral, is the promotion of *P. acnes* resistance. Benzoyl peroxide has a broad-spectrum bactericidal action, which does not select for resistance during long-term use. It is therefore recommended that it is used intermittently during courses of antibiotics, to eliminate any resistant propionibacteria [87,88].



**Table 19.2** Benzoyl peroxide (BP) dose–response RCTs.

First author, ref.	Comparators	Patients (n)	Severity	Duration (weeks)	Blinding	Outcomes	Comments
Mills (1986, 2) [70]	1. BP 2.5% 2. BP 5%	53	1/2	8	P, A	Equivalent efficacy and burning, peeling and erythema; ILs: 56% vs 58% reduction	2 LTF; not clear if randomized
Mills (1986, 3) [70]	1. BP 10% 2. BP 2.5%	50	1/2	8	P, A	Equivalent efficacy but 10% more burning, erythema and peeling. ILs: 45% vs 47% reduction	No LTF; not clear if randomized
Yong (1979) [76]	1. BP 2.5% 2. BP 5%	200	1/2/3	4–18	0	>50% reduction in lesion counts 64/96 vs 74/98 (no SSD); erythema 45 vs 50; desquamation 22 vs 28; itching/burning 16 vs 10; no SSD overall	Variable duration of treatment
Handojo (1979) [62]	1. Tretinoin 0.05% 2. BP 5% 3. BP 10% 4. Tretinoin 0.05%/BP 5% 5. Tretinoin 0.05%/BP 10%	250	1/2/3	10	0	Overall change greater in 5% combination group; rate of local intolerance 20% in both groups, but greater in 10% group; >50% reduction in NILs: 34/47 vs 37/45 vs 33/47 vs 45/50 vs 44/50; >50% reduction in ILs: 27/36 vs 34/42 vs 28/41 vs 34/44 vs 39/49; no SSD between BP concentrations	11 LTF; not ITT; 47 patients reactions
Marsden (1985) [230]	1. BP 5% 2. BP 5%/0.5 g OT 3. BP 5%/1 g OT 4. BP 5%/1.5 g OT	82	1/2/3	16	A	Patient adequate response: 2/23 vs 6/24 vs 8/19 vs 12/17; 10 BP patients local intolerance; ILs: 56 vs 70 vs 75% vs 78% reduction	Assume randomized but not stated; previous failure to treatment; 10 LTF; not ITT
Fyrand (1986) [297]	1. BP 5% (alcohol) 2. BP 5% (water)	48	—	8	P, A	No difference in clinical effect, but less irritation with water-based preparation	Abstract only

Severity: 1, mild; 2, moderate; 3, severe. Blinding: 0, open; A, assessor; P, patient. BP, benzoyl peroxide; LTF, lost to follow-up; ITT, intention-to-treat; ILs, inflamed lesions; NILs, noninflamed lesions; SSD, statistically significant difference.

### Implications for practice

Benzoyl peroxide alone or in combination with other topical treatments is the standard of care for mild to moderate acne vulgaris, as a result of its activity against both ILs and NILs. Some individuals find benzoyl peroxide highly irritating on initial application. Tolerance is generally developed with prolonged exposure, and individuals should be counseled accordingly. Low-strength benzoyl peroxide is recommended, as higher strengths are more of an irritant and there is no evidence to suggest that 10% in general is more effective than 5%. Recent evidence suggests that newer delivery systems may mitigate intolerable side effects. It is common practice for patients to apply benzoyl peroxide to individual lesions alone; clinicians should advise patients to apply it in a thin layer to all areas to prevent the formation of new lesions.

### Salicylic acid

Salicylic acid is an exfoliant and chemical irritant.

#### Efficacy

The AHRQ review [14] located three RCTs (Table 19.3) [88–90]. Two percent salicylic acid was more effective in reducing all lesion types than the alcoholic lotion vehicle at 12 weeks in 114 paired individuals with mild to moderate acne [88]. The second study enrolled 30 individuals and had major losses to follow-up [90]; 1.5% salicylic acid was more beneficial than placebo. One further crossover RCT in 30 individuals with mild acne compared a 2% cleanser with a 10% benzoyl peroxide facial wash; neither product was therefore in prolonged contact with the skin [89]. The results of the study cannot be considered as valid evidence, however,

because the trial was only 4 weeks in total and there was no wash-out period between the 2-week treatment periods.

#### Adverse effects

Salicylic acid is known to cause skin irritation that presents as erythema, dryness, and peeling; this was evident in the RCT evidence located.

### Implications for practice

There is no evidence to support the routine use of salicylic acid in preference to other topical therapies.

### Azelaic acid

Azelaic acid has been shown to normalize the increased keratinocyte production and keratinization associated with acne and to inhibit *P. acnes* [91]. A direct anti-inflammatory effect has also been demonstrated [92].

#### Efficacy

The AHRQ review [14] located eight RCTs of azelaic acid in mild to moderate acne (Web Table 19.3). The comparators used were placebo [93], vehicle [94], benzoyl peroxide [77], tretinoin [94], oral tetracycline [95,96], and in combination with glycolic acid versus tretinoin [97]. One further RCT published in German evaluated its efficacy against 2% erythromycin [98,99].

In papulopustular acne, 20% azelaic acid has similar efficacy at 5 or 6 months to 0.05% tretinoin [94], 5% benzoyl peroxide [80], 2% topical erythromycin [99], and oral tetracycline 1 g/day [95,96], with consistent percentage reductions in median ILs of 80–84%. In

Table 19.3 RCTs of salicylic acid.

First author, ref.	Comparators	Patients (n)	Duration (weeks)	Severity	Blinding	% decreased NIL	% decreased IL	Outcomes	Comments
Shalita (1981) [89]	1. Salicylic acid 2% cleanser	30	2 + 2	1/2	0	34		No side effects reported	Crossover; no wash-out period; no LTF; results not valid as phase 1 only 2 weeks and no wash-out period; BP group higher NIL count at baseline; short contact
	2. BP 10% wash					20			
Eady (1996) [66]	1. Salicylic acid 2%	114	12	1/2	A,P	46*	28*	1 > 2 all lesions; irritant dermatitis both groups but greater incidence in 1; percentage decrease total lesions: 40 vs 16*	15 LTF; not ITT; both in alcoholic lotion
	2. Vehicle					26	9		
Roth (1964) [90]	1. Salicylic acid 1.5%	30	10	1/2	0			Salicylic acid reported as greater reduction, but no intergroup comparison; burning in 10/15 in salicylic acid group	
	2. Placebo								

\* Statistically significantly superior ( $P < 0.05$ ).

Severity: 1, mild; 2, moderate; 3, severe. Blinding: 0, open; A, assessor; P, patient; BP, benzoyl peroxide; LTF, lost to follow-up; ITT, intention-to-treat; ILs, inflamed lesions; NILs, noninflamed lesions.

comedonal acne, 20% azelaic acid had similar activity to 0.05% topical isotretinoin, with 79% and 82% reductions in comedonal counts, respectively. A multicentered RCT of 150 patients with mild-to-moderate acne compared 5% azelaic acid and 2% azelaic acid/clindamycin combination. The combination therapy showed a significant reduction in acne severity index (64.16%) compared with either 5% azelaic acid (32.46%) or clindamycin monotherapy (47.73%) after 12 weeks [100]. Similarly, combination 5% azelaic acid and 2% erythromycin yielded significant lesion reduction compared with azelaic acid or erythromycin monotherapy [101].

### Adverse effects

In common with other topical agents, azelaic acid induces cutaneous reactions, which occur in approximately one-third of individuals [99]. The incidence is highest in the first 4 weeks of therapy and, in the RCTs examined, only 5–10% of reactions were categorized as “marked.” In the clinical studies, which also included postmarketing evaluations, 0–5% of individuals experienced scaling, 5–23% burning, and 13–29% itching. Azelaic acid is not known to cause photosensitivity, and sublethal doses do not promote *P. acnes* resistance [102]. Azelaic acid is better tolerated than benzoyl peroxide [80] and tretinoin [94,97], and it does not bleach clothing or hair. It is used in hyperpigmentary skin disorders, but has not been shown to have depigmentary effects in acne patients [102], suggesting that it preferentially targets abnormal melanocytes.

### Comments

There are no known incompatibilities between azelaic acid and other topical anti-acne agents.

### Implications for practice

Azelaic acid is an effective therapy for mild to moderate papulopustular acne and as effective as 0.05% isotretinoin in comedonal acne. The onset of action is slower than that seen with benzoyl peroxide. Patients should be counseled to expect a delayed response. Anecdotal reports have suggested that azelaic acid may reduce the incidence of postinflammatory hyperpigmentation, which is possibly attributable to its activity on abnormal melanocytes [103]. Darker skinned patients should be monitored for signs of hypopigmentation.

### Summary

All of the agents reviewed are effective in the treatment of mild and moderate acne vulgaris. There are very few data to support the use of one agent over another, and there has only been one RCT on the use of the agents in combination, which showed that benzoyl peroxide and tretinoin in combination are superior to either agent alone [62]. Adapalene is better tolerated than tretinoin, and the RCT evidence reviewed suggests that azelaic acid may be better tolerated overall than other agents, but there will be considerable variation between individual patients. A number of RCTs compare these agents against and in combination with topical antibiotics; these are considered in the next section.

### What is the role of antibiotics in the management of acne vulgaris?

The role of antibiotics in the management of acne is still debated, and although much evidence has been collected on the efficacy of individual agents, there are very few good-quality comparative data. Oral antibiotics were used initially in the 1950s because it was assumed that acne occurred as a result of bacterial infection. Whilst activity against *P. acnes* has been clearly demonstrated, there is evidence of an anti-inflammatory effect [104], which is still being investigated.

Three systematic reviews provided evidence on the role of antibiotics [14,105,106]. The conclusions of the AHRQ review are based only on comparisons, where there are at least two trials of acceptable quality showing moderate to strong statistical evidence for a clinically meaningful end point and effect. Of the oral antibiotics, the only clear evidence was located for tetracycline. Topical clindamycin and erythromycin were superior to vehicle in the treatment of mild to moderate acne, and topical tetracycline was ineffective. The Cochrane review [105] of minocycline examined 27 RCTs and concluded that while minocycline is likely to produce similar outcomes to other first-generation and second-generation tetracyclines, it should not be used as a first-line agent, because of uncertainty over its safety and higher cost in comparison with older tetracyclines. There was no evidence to suggest that it is superior to other tetracyclines, and its efficacy relative to other acne therapies could not be reliably determined because of inadequacies in

the studies examined. The third systematic review [106] evaluated all randomized and nonrandomized clinical trials ( $n = 45$ ) investigating topical therapy with erythromycin or clindamycin alone for inflammatory acne. A significant decrease in the treatment effect of topical erythromycin occurred over time, suggesting the development of antibiotic resistance.

### Oral antibiotics

The AHRQ report reviewed 11 placebo-controlled trials of oral antibiotics [107–117], and five others were located by searches [118–122] (Web Table 19.4). All but five RCTs investigated tetracycline; one evaluated minocycline, two doxycycline [123], one roxithromycin [120], and one lymecycline [121]. All were double-blinded, and most included patients with moderate to severe acne. Only five provided data at 12 weeks or more [110,113,114,121,122], and only four included more than 50 patients in each arm [114,116,118,121]. Tetracycline at total daily doses of 500 mg and 1 g was consistently superior to placebo in terms of overall grade and reduction in ILs. Lymecycline 150 mg b.i.d. and lymecycline 300 mg q.o.d. were equally efficacious in the treatment of moderate to severe acne, and both were superior to placebo at all points during a 12-week study [121]. A small RCT ( $n = 46$ ) reported a significant decrease in median acne scores in comparison with placebo in patients taking roxithromycin 150 mg b.i.d. during the 10-week study. Data on NILs were from two doxycycline RCTs [122,123]. One reported comparable efficacy [123] at 4 weeks, but this is expected, given the delayed onset of activity associated with oral antibiotics. A second RCT designed to evaluate subantimicrobial dosing of doxycycline (20 mg b.i.d.) showed statistically significant decreases in ILs, including an 84% reduction in papules and a 90% reduction in pustules at 3 months [124].

Nine head-to-head RCTs of the currently used oral antibiotics were included in the AHRQ review [125–133]; the Cochrane review located a further nine [134–142], and further search located three additional studies [143–145] (Web Table 19.5). The majority of the trials had problems with design and execution. No oral antibiotic was demonstrated to be superior to any other, although equivalence cannot be conclusively stated, as none of the studies was adequately powered to demonstrate it. Percentage reductions in ILs were consistently greater than 50% at 12 weeks. Percentage reductions in NILs were more variable, with only three RCTs reporting more than 50% reductions at 12 weeks [139,142,144]. The results consistently showed an improvement in 70–90% of individuals at 12 weeks. A recent multicenter RCT showed that minocycline 100 mg daily, roxithromycin 150 mg b.i.d., and faropenem 200 mg t.i.d. were equally as efficacious in terms of IL reduction and safety after 8 weeks in patients with moderate-to-severe acne [145]. Similar to previous studies, this RCT was not adequately powered to evaluate equivalence. Conversely, a systematic review of 57 RCTs demonstrated a high-quality analysis of oral tetracyclines and showed equal efficacy in the reduction of both NILs and ILs [146].

### Topical antibiotics

The AHRQ review located 31 RCTs comparing a topical antibiotic with its vehicle, and a further eight RCTs were located by independent searches (Web Table 19.6). Nine of the RCTs also included other comparators. The antibiotics investigated were clindamycin (13 RCTs) [75,115,116,147–156], erythromycin (14 RCTs) [157–165], erythromycin/zinc (three RCTs) [117,166,167], 2% fusidic acid (two RCTs) [168,169], meclocycline [170], metronidazole [171], triclosan [172], and tetracycline (three RCTs) [112–114]. Among

the studies for which details were available, all but two used twice-daily application [75,156]. Many of the studies were underpowered to conclusively state that there were no significant differences between the comparators. A systematic review [106] designed to assess the efficacy of the topical antibiotics erythromycin and clindamycin over time included 45 studies: 22 double-blind ITT studies, 10 placebo-controlled trials, 12 single-blind trials, and 1 open, randomized trial. The duration of treatment in the trials included varied between 8 and 12 weeks for erythromycin and between 8 and 16 weeks for clindamycin, with 12 weeks being most common for both medications. Erythromycin concentrations varied in studies from 1.5% to 4% (most common concentrations were 1.5% and 2%), while clindamycin concentrations remained stable during the analysis period at between 1% and 1.2%. Comparisons of studies longitudinally only included trials using the same antibiotic dosage.

The AHRQ review concluded that although clindamycin tended to produce greater reductions in ILs than its vehicle, the results were rarely statistically significant; global measures more consistently indicated superiority to placebo. The evidence available does not support the effectiveness of clindamycin against NILs. Erythromycin similarly had a greater impact on ILs. A 12-week study of clindamycin 1% foam versus clindamycin 1% gel applied once daily also included vehicle comparators [156]. This study reported a statistically significant advantage in total lesions, ILs, and NILs with foam over gel and superior efficacy in comparison with the vehicle. A 24-week study of 2% erythromycin gel versus vehicle, designed primarily to detect bacterial resistance to treatment over time [165], found no difference in acne outcomes at any point during the study. Highly resistant erythromycin-specific susceptibility profiles were found among patients randomly assigned to the erythromycin treatment arm. Fusidic acid was more active than vehicle against ILs at 6 weeks in one study, but not at 12 weeks in a second study, which also did not show any difference in its activity against NILs. The two meclocycline studies also showed decreases in ILs, with no data for NILs. The 0.75% metronidazole RCT showed that it was no more active than placebo in mild to moderate acne, producing statistically significant reductions in neither ILs nor NILs. The three tetracycline RCTs demonstrated that 0.5% tetracycline was approximately 50% more active than vehicle in terms of change in acne grade from baseline, although no intergroup statistical analyses were performed. Only one trial provided data on differential lesion counts; the results suggested again that tetracycline was active against ILs but not NILs. In the larger RCTs, a 55–60% mean reduction in ILs was consistently seen at 12 weeks [14].

The AHRQ review located 14 head-to-head trials of topical antibiotics, and further search yielded four additional RCTs (Web Table 19.7). There were no differences in efficacy between clindamycin hydrochloride and phosphate [150,151,155], or between different formulations [154,173,174] in the six RCTs examined in the AHRQ. One RCT did demonstrate a difference between clindamycin formulations, showing clindamycin 1% foam to be superior to clindamycin 1% gel for reduction of total lesions, ILs, and NILs at 12 weeks [156]. Four large RCTs [167,175–177] and one smaller study [178] compared clindamycin and erythromycin. Several trials reported differences between topical antibiotics for certain outcomes at certain time points, though there were no consistent differences overall. Topical 0.3% ciprofloxacin showed greater efficacy to 4% erythromycin in percentage pustule reduction over 6 weeks, providing evidence for an alternative topical therapy when bacterial resistance is considered [179]. Similar efficacy of topical fluoroqui-

nolones in mild to moderate acne was demonstrated in an RCT comparing 1% nadifloxacin cream with 4% erythromycin gel [180]. In comparison with tetracycline, two studies [181,182] reported insignificant or inconsistent differences in lesion counts. However, both trials demonstrated a significant difference in favor of clindamycin in terms of acne severity or improvement. No difference between clindamycin and nicotinamide was shown in the RCT located, but it was underpowered to conclusively state equivalence [183]. An additional 12-week RCT [184] compared a 2% topical azithromycin preparation with a 2% topical erythromycin. Comparable decreases in ILs counts were seen in both groups, though the study was underpowered and not placebo controlled. One systematic review [106] evaluated RCTs comparing the efficacy of erythromycin versus clindamycin. Though topical erythromycin remains a viable treatment option, a significant decrease in efficacy has occurred over time (1974–2002), while the efficacy of topical clindamycin remained stable.

### Oral versus topical antibiotics

The two systematic reviews located also provided comparative data on the use of oral versus topical antibiotics [14,105]. A number of other nonsystematic reviews and individual RCTs were also located, giving a total of 21 studies [161,185–198], six of which also included a placebo control arm [112–117] (Web Table 19.8). Twelve used double-dummy designs to maintain blinding. Oral antibiotics have a delayed onset of activity; studies of shorter duration may therefore be biased in favor of the topical agent.

The evidence from three RCTs suggests that minocycline, 50 mg twice daily, produces results against both NILs and ILs that are comparable with 1% clindamycin applied twice daily [191,193]. All but one trial [198] enrolled fewer than 100 patients, and they were therefore underpowered to conclusively state equivalence.

Six RCTs compared oral tetracycline 250 mg twice daily with 1% clindamycin twice daily [115,116,161,185,187]. Only one RCT was longer than 8 weeks in duration [187], and only one study was adequately powered (305 patients), but it was of inadequate duration [116]. This study found that at 8 weeks there was no significant difference in the percentage reductions obtained with either tetracycline 250 mg twice daily or 1% clindamycin applied twice daily in pustules (68% vs 76%) and papules (63% vs 68%) in patients with moderate to severe acne. However, the physician rated the clindamycin therapy as good to excellent in a greater number of cases: 86 of 105 in comparison with 66 of 103 ( $P < 0.05$ ). Four of the other studies failed to detect any significant differences between the therapies, with the fifth finding that clindamycin caused significantly greater percentage reductions in ILs (57% vs 72%;  $P < 0.001$ ) at 8 weeks in patients with mild acne [115]. The 12-week study found no difference [187].

Tetracycline, 250 mg twice daily, produced similar changes in lesion counts at 12 weeks to topically applied 1.5% erythromycin in a single RCT of 54 patients with moderate to severe acne [190]. Although erythromycin produced greater percentage changes numerically, these were not significant. None of the four RCTs located found any differences in overall grade between oral tetracycline, 250 mg twice daily, and topically applied 1.5% meclocycline twice daily; both were superior to placebo in the three studies that also used a placebo control [189]. None of the studies used ITT analysis. At 8–12 weeks, oral tetracycline 250 mg twice daily was found to produce similar reductions in overall grade to topical 0.5% tetracycline, with one trial finding no effect on comedones [112–114].

### Combination therapy

A number of RCTs have investigated oral and topical antibiotics either against or in combination with other agents (Web Table 19.9), the rationale for this being that treatments that attack more than one factor implicated in the pathogenesis of acne will be more effective. The different mechanisms of action are summarized in Table 19.4 [199].

### Efficacy

Two RCTs were located that compared an oral antibiotic with benzyl peroxide [196–198]. Although one study was underpowered to conclusively state equivalence, similar efficacy was found between 5% benzyl peroxide and oral oxytetracycline, 250 mg twice daily, at 6 weeks [197]. The oral agent was more effective against acne of the trunk. A large ( $n = 649$ ) randomized 18-week study compared five antibacterial regimens: oxytetracycline plus topical placebo; oral Monocline (doxycycline) plus topical placebo; topical benzyl peroxide plus oral placebo; topical erythromycin and benzyl peroxide combination plus oral placebo; and topical erythromycin and benzyl peroxide separately plus oral placebo [198]. Topical benzyl peroxide and benzyl peroxide–erythromycin combinations showed similar efficacy to oral oxytetracycline and minocycline.

The AHRQ review located eight RCTs that compared topical antibiotics with 5% benzoyl peroxide, and searches found one additional trial [75,164,196,200–204]. In the three RCTs located, 5% benzoyl peroxide was found more active against NILs in moderate acne than 1% clindamycin [75,200,201] over 10–12 weeks. Two studies also found that it was more active against ILs [200,201], although the third found no difference [75]. Benzoyl peroxide was also more active against both NILs and ILs than 1% meclocycline [203]. Compared with erythromycin, benzoyl peroxide was more active against NILs and similarly active against ILs [164,202]. All RCTs providing data showed that benzoyl peroxide caused more local irritation.

Three RCTs compared 20% azelaic acid with oral tetracycline (variable dose) [95,96] in patients with mild to severe acne. No significant differences were reported in any lesion counts, except in the smallest trial, which was very small and suffered from high drop-out rates in the azelaic acid group. A 20-week RCT of 20% azelaic acid in comparison with 2% topical erythromycin was located through additional searches [98]. No differences between the comparators were found.

**Table 19.4** Targets of acne therapies.

	Sebum excretion	Keratinization	Follicular <i>P. acnes</i>	Inflammation
Benzoyl peroxide	–	(+)	+++	(+)
Tretinoin	–	++	(+)	–
Clindamycin	–	–	++	–
Antiandrogens	++	–	–	–
Azelaic acid	–	++	++	+
Tetracyclines	–	–	++	+
Erythromycin	–	–	++	–
Isotretinoin	+++	++	(+)	++

**Source:** Gollnick, 1990 [199]. Adapted with permission from Taylor & Francis.



### Use of combination therapies

Twelve RCTs were located that examined combinations of 0.025% tretinoin and 1–1.2% clindamycin against either tretinoin, clindamycin [205,206], or both [207–211] (Web Table 19.10). One additional RCT compared a combination 2% erythromycin–0.05% tretinoin against each agent individually [212]. The combination therapy clindamycin–tretinoin produced a greater reduction in NILs and ILs, though statistical significance was only reached with clindamycin and tretinoin monotherapy, respectively [205,206,210,211]. Three additional studies evaluated the role of adding benzoyl peroxide to a tretinoin and clindamycin regimen. One study reported similar efficacy and improved tolerability of clindamycin–benzoyl peroxide compared with clindamycin–benzoyl peroxide in the morning plus tretinoin and clindamycin in the evening [209]. The two remaining studies showed that clindamycin–benzoyl peroxide induced a more rapid clearance of NILs and ILs [213] as well as reduced *P. acnes* colonization and antimicrobial resistance [214] compared with a benzoyl peroxide-deficient clindamycin and tretinoin scheme.

Four trials compared 0.1% adapalene plus antibiotic combinations to antibiotic alone [215–218]. In the first trial of 242 patients with moderate to severe acne, adapalene plus 300 mg of lymecycline showed a greater reduction in NILs and ILs at 12 weeks than lymecycline plus vehicle. Side-effect profiles were similar for both treatment groups [215]. The second trial included 467 patients with severe acne who were randomly assigned to either the adapalene plus doxycycline group or doxycycline treatment alone for 12 weeks. Percentage reductions in NILs were 60% and 41% respectively [216]. There was also a greater reduction in the combination group for ILs (65% vs 59%). Both treatments were well tolerated. The third and fourth trials compared the efficacy of clindamycin alone and in combination with adapalene in a total of 549 patients with mild to moderate acne [217,218]. Both trials showed significant reductions in NILs and ILs in the combination group by week 12. The fourth trial also demonstrated a significant reduction in all lesion counts during the maintenance phase in patients receiving adapalene (42%) in comparison with an increase for all lesion counts in the control group (92.1%). A fifth trial that compared a retinoid in combination with an antibiotic with 5% benzoyl peroxide in combination with 3% erythromycin in 188 patients with mild to moderate acne showed comparable efficacy after 12 weeks [219].

One 12-week RCT compared topical 5% dapsone gel plus 0.1% tazarotene cream with tazarotene monotherapy [220]. Though both combination and monotherapy demonstrated a significant reduction in lesion count from baseline, the combination therapy showed a greater reduction in NILs while maintaining a similar side-effect profile. This study provides moderate evidence for the use of dapsone–tazarotene combination in early comedonal acne. No patients experienced systemic side effects of dapsone.

A trial that compared a hydrogen peroxide cream and 0.1% adapalene gel combination with a benzoyl peroxide cream and adapalene gel combination showed equivalent reductions in NILs [221]. Significant reductions in ILs and better tolerability were noted for the hydrogen peroxide plus adapalene group at week 8 in patients with mild to moderate acne. The use of adapalene and benzoyl peroxide alone and in combination reduced NILs and ILs at 24 weeks, with no significant differences in erythema, dryness, or burning.

Combinations of antibiotics and benzoyl peroxide were examined in 10 RCTs (Web Table 19.11); the antibiotics were clindamycin [75,191,222], erythromycin [164,223–226], meclocycline [203], dapsone, and metronidazole [204]. In the seven studies that used

an antibiotic alone as a comparator, the combination was more active against both ILs and NILs [75,164,200,222,223,227]. In the seven studies that used benzoyl peroxide alone as a comparator [75,164,200,203,204,226], the data were equivocal; some studies showed a greater effect for the combination therapy while others showed no statistical difference [75,164,200,203,204,222,226]. The most recent study showed similar side-effect profiles between the combination therapy and the monotherapies [222]. The trial comparing 5% dapsone gel plus benzoyl peroxide with dapsone plus moisturizer showed no statistical difference in reduction of ILs [228]. Combination 5% benzoyl peroxide–3% erythromycin has greater activity against *P. acnes* than 3% erythromycin monotherapy and results in significantly greater clinical improvement [88]. One 8-week RCT [229] of 327 patients with moderate to severe acne demonstrated that a new single-use erythromycin–benzoyl peroxide formulation reduced acne lesions in terms of the physicians' global acne severity scores and the patients' end-of-treatment global assessment of improvement. Since refrigeration is not required, patients can mix the two gels in the single-use package and eliminate the need for a compounding pharmacist.

Another study compared 5% benzoyl peroxide plus 2% metronidazole against an oral antibiotic (oxytetracycline); however, the results of this trial were unfairly biased against the oral antibiotic due to the short 6-week duration of the study [204]. Another RCT of adequate duration (16 weeks) compared concomitant 5% benzoyl peroxide with an oral antibiotic (oxytetracycline 0.5 g, 1 g, and 1.5 g), but this study did not clearly state whether or not patients were randomized to treatment [230]. The response was considered adequate in 2 of 23 patients with 5% benzoyl peroxide monotherapy and in 6 of 24, 8 of 19, and 12 of 17 patients using 5% benzoyl peroxide plus oxytetracycline 0.5 g, 1 g, and 1.5 g, respectively. A recent RCT suggested the addition of levamisole to doxycycline regimens for severe nodulocystic acne [231]. The patients receiving doxycycline 100 mg daily plus levamisole 2.5 mg/kg per week demonstrated a significant decrease in ILs (nodules+cysts: 90%) as well as acne severity index (82.2%) compared with doxycycline monotherapy (nodules+cysts: 58%; acne severity index: 67.95%).

Few studies have compared oral antibiotic treatment regimens with oral retinoids. A recent 6-month RCT with a 2-month follow-up compared oral tetracycline plus topical adapalene with oral isotretinoin [232]. Though both arms led to decreased NILs and ILs from baseline, oral isotretinoin demonstrated an increased reduction of NILs and superficial ILs while maintaining a prolonged improvement after treatment cessation. Nonetheless, oral tetracycline plus topical adapalene was revealed as a comparable treatment option if oral retinoids are contraindicated.

### Harms

All antibiotics are associated with individual side effects that are well documented and must be considered. The potential systemic side effects are theoretically reduced by topical application, as usually less than 10% absorption occurs [233]. However, prolonged and extensive application to the skin, which is a good medium for gene exchange amongst bacteria [234], may facilitate the spread of resistance [235]. This has implications for clinical practice, as *P. acnes* resistance is associated with a poor therapeutic response to antibiotics, and the efficacy of some antibiotics is decreasing over time. Of greater importance, however, is the spread of resistance to other microorganisms, and there have been calls for policies to restrict the prescribing of antibiotics in acne [87,236]. In particular, studies have shown that both *P. acnes* and *Staphylococcus epidermidis* can transfer antibiotic resistance to *Staphylococcus aureus*



[83]. One systematic review examined *P. acnes* resistance to systemic antibiotics [237]. The 12 articles examined demonstrated an overall increase in *P. acnes* resistance, from 20% in 1978 to 62% in 1996. Resistance was most commonly reported to erythromycin, clindamycin, tetracycline, doxycycline, and trimethoprim; resistance to minocycline was rare. The authors concluded that long-term rotational antibiotics are inappropriate and that treatment should be adjusted when therapeutic failure becomes evident. Antibiotic–benzoyl peroxide combination therapies can be useful, as these regimens were not affected by *P. acnes* antibiotic resistance [198], and have been shown to reduce the concentration of antibiotic-resistant *P. acnes* on the skin prior to treatment and the emergence of new antibiotic-resistant *P. acnes* posttreatment initiation [83,214].

### Comment

A proportion of individuals fail to respond to antibiotics; epidemiological studies have estimated that the figure is between 10% [238] and 17% [239] of individuals. Theories that have been proposed include individual differences in the absorption, distribution, and elimination of the antibiotic, as well as poor compliance, the follicular microenvironment, and *P. acnes* resistance [238]. The underlying severity of the disease may also determine the response to antibiotics, as severe acne and acne of the trunk have been shown to respond less well than moderate acne [239,240], possibly as a result of the higher sebum excretion rate (SER) [241] diluting follicular drug concentrations [238]. Clinically, another important impact of alteration in cutaneous microflora is the possibility of Gram-negative folliculitis developing, which presents with profuse superficial pustules around the nose and deep cystic lesions on the face and neck, usually colonized by *Proteus*, *Enterobacter*, or *Klebsiella* species [242].

### Implications for practice

There is no conclusive evidence of the superiority of one antibiotic over another, nor of any advantages for either oral or topical application. The choice of agent should, therefore, be based on the patient's preference, with consideration of the individual side effects of the antibiotics and the cost. The formulation of the topical antibiotic may also be important – for example, alcohol bases are likely to be more drying and, therefore, more suitable for oilier skins. Patients with more extensive disease, particularly those with acne of the trunk, may prefer oral treatment rather than having to apply topical agents to extensive areas. It is vital that patients should be properly counseled on how to use their medication, as inappropriate use has been shown to reduce effectiveness [230].

Second-generation tetracyclines – such as minocycline, doxycycline, and lymecycline – have been described as being more active, because their greater lipophilicity results in greater sebum penetration and PSD concentration. This review has not found any evidence to support this, and their superiority has not been demonstrated. These agents are easier for patients to take, however, as they can be taken once daily and the absorption may be less affected by food [243–245]. However, tetracycline need not be taken four times a day: its half-life of approximately 9 h in plasma is likely increased in the skin. Furthermore, subantimicrobial doses of doxycycline may be as effective as standard dosages. Maintaining serum antibiotic concentrations at steady state does not appear necessary for clinical efficacy or moderating anti-inflammatory effects.

It is recognized that antibiotics have less activity than other agents against NILs, which makes them less suitable for use in

patients with primarily noninflammatory acne. The evidence for the comparative efficacy of antibiotics and benzoyl peroxide against ILs is equivocal, and further research is required to establish their relative place in acne therapy. The studies reviewed found that combinations of antibiotics with benzoyl peroxide were more effective than antibiotics alone, which can probably be attributed in part to the lack of activity of antibiotics against NILs. However, the irritancy of benzoyl peroxide may make it unacceptable to some patients. There is no compelling evidence for the combined use of antibiotics and retinoids. There is no benefit in concomitant use of oral and topical antibiotics, and this practice may select for resistant strains. Intermittent use of benzoyl peroxide is recommended during extended antibiotic therapy, to eliminate any resistant strains [246]. If antibiotic resistance is a major concern, another viable option would be to discontinue antibiotics altogether and start a combination topical therapy, such as benzoyl peroxide and a topical retinoid [247]. Though the evidence is sparse, this approach has been shown to reduce antibiotic-resistant *P. acnes* after 4 weeks of treatment [247].

### What dose of oral antibiotics should be prescribed?

Historically, antibiotics have been used for the treatment of acne vulgaris at doses that are lower than those used for other infections. Although the exact origin and rationale of this convention is not known, the most likely explanation is that doses were reduced initially in response to concerns over maintaining patients on high-dose antibiotics for long periods of time. When it was subsequently observed that lesions did not recur when the dose was reduced and that patients relapsed as soon as therapy was discontinued, dose reduction would have become standard practice [248]. Low doses of antibiotics were therefore used in early trials [110,119,249,250]. Guidelines recommended that full antibiotic doses should be used initially for 3–4 weeks and then reduced gradually until the patient can be maintained on the lowest possible dose [251,252]. Despite the fact that there are no adequate dose–response studies to support it, this use of low-dose antibiotics has remained standard practice for many years.

Only four RCTs were located that investigated the use of different doses of antibiotics. One study failed to find any clinical difference after 8 weeks of therapy between patients maintained on an initial starting dose of minocycline 100 mg daily and those in whom the initial dosage was reduced to 50 mg daily after 4 weeks [253]. Minocycline may not be typical of all antibiotics, however, because there is considerable variation between individuals in the serum levels attained after oral administration [254]. Eight weeks may also be an inadequate period to examine comparative efficacy. In the second study, roxithromycin 300 mg was more effective than 150 mg over 8 weeks in 30 patients with severe acne [255]. A third study evaluated subantimicrobial doses of doxycycline (20 mg b.i.d.) in comparison with placebo for 6 months and found statistically significant decreases in combined IL and NIL counts, total lesion counts, and comedones in patients randomly assigned to doxycycline [122]. The fourth study also evaluated subantimicrobial doses of doxycycline (20 mg b.i.d.) and found noninferior efficacy compared with conventional dosing (100 mg daily) with respect to IL reduction after 3 months in patients with moderate acne [124]. These patients, however, were not followed to investigate the period of time before their next breakout, which deems this study of limited clinical significance.

Other evidence located included a series of nonrandomized studies in 420 individuals with moderate to severe acne. In a

nonrandomized controlled study of 152 patients matched for age, sex, site of involvement, and severity, those maintained on erythromycin, 1 g daily, and 5% benzoyl peroxide showed a significantly greater response in comparison with those receiving 0.5 g and 5% benzoyl peroxide. The improvements in acne grade at 6 months were 35% and 79% in men and 59% and 79% in women. The relapse rates within 1 year were also significantly lower in the high-dose group: 31% versus 60% in women and 82% versus 39% in men. A similar group of 296 patients did not show higher rates of gastrointestinal side effects at the higher dose [239]. Individuals with severe acne, acne of the trunk, and high SERs responded less well to combined treatment with 5% benzoyl peroxide and erythromycin 250 mg twice daily over 6 months [239].

There are also reports in the literature that higher daily doses of tetracycline [256] and oxytetracycline [230] are more effective in patients with severe acne or acne that is recalcitrant to standard therapy. The results of these studies are questionable, however, as both have serious methodological flaws and used concomitant topical therapy. A cohort of 80 patients with nodulocystic and conglobate acne who had not responded to standard antibiotic doses showed improvement with 1.5–3.0 g tetracycline [257]. A second similar cohort of 31 patients with severe acne or acne resistant to standard-dose antibiotics received up to 3.5 g with concomitant topicals, and 27 of the patients showed great improvement. Fifteen individuals suffered adverse events and two had to discontinue therapy because of raised serum creatinine phosphokinase, emphasizing the need for ongoing renal and hepatic monitoring. The onset of improvement ranged from 1 to 6 months. Flare occurred in nine patients on reduced dose, despite the use of topicals [256].

A prospective case series of 68 patients with moderate to “cystic” acne, in whom the dose was titrated according to the response, found that in a period of up to 2.5 years, 51 of the 58 patients who improved required only 250 mg tetracycline daily [250]. Increased severity of acne was an indicator for higher dose and nonresponse. In 10 cases, tetracycline had no effect, regardless of dose.

### For how long should antibiotic therapy be continued?

This question was not addressed in either of the systematic reviews, and no specific RCT evidence was located. The literature contains a number of recommendations, few of which are backed by hard evidence. The consensus of opinion is that although the effects of antibiotics on ILs are visible after a few days, a minimum of 3 weeks is required before any improvement can be categorically stated [114,252], and therapy should therefore be continued for a minimum of 3 months, and 6 months for maximum benefit [1]. As antibiotics do not expel existing comedones, the effect on these lesions only becomes evident after a few months of continual use; it takes approximately 8 weeks for a microcomedo to develop into a visible lesion. Relapse occurs in nearly half of the patients up to 8 weeks after stopping therapy [258], necessitating additional courses [259]. In patients who relapse immediately, the antibiotic used should be rotated every 6 months [260]. Two RCTs that included intermediate assessments showed that improvement continued beyond 4–6 weeks to 3 months [110,129].

An observational cohort study of 543 patients with moderate acne who were treated with erythromycin, 1 g/day, combined with 5% benzoyl peroxide suggested that the median percentage improvement at 6 months was 78% (interquartile range 67–90%); 408 of 492 individuals showed an over 50% reduction in acne grade; 247 of 279 who continued with benzoyl peroxide alone maintained

improvement; 174 individuals who continued with combination for a further 6 months showed no additional benefit, but this group also included a subgroup of responders, nonresponders, and those switched to alternative antibiotics. Therapy was continued in 31 patients who had not shown 50% improvement within the 6-month period; the percentage improvement was greater in the 29 individuals treated with minocycline.

### What is the role of oral isotretinoin in the treatment of severe acne?

Severe, treatment-resistant acne is frequently treated with oral isotretinoin. Although its complete mechanism of action has yet to be elucidated, oral isotretinoin has been shown to decrease sebum excretion, keratinization, inflammation, and follicular colonization by *P. acnes* and other organisms, such as *Pityrosporum* spp.

#### Efficacy

The efficacy of systemic isotretinoin in the treatment of severe, cystic acne is well demonstrated. The AHRQ systematic review identified 11 RCTs which evaluated the outcomes of isotretinoin therapy [261–271]. One trial [271] used SER as its only measure of drug efficacy, and included no results regarding clinical outcome (number of lesions, summated cyst diameter, severity of disease, etc.). It was therefore excluded from the RCTs listed (Web Table 19.12). Three other trials [272–274] were found through searching PubMed. At least nine of the 13 RCTs were investigator blinded, with three of the remaining four not indicating any blinding protocol.

Five RCTs [262,263,268,270,273] compared isotretinoin therapy with placebo or other traditional, first-line therapies (etretinate, tetracycline, dapsone, minocycline). In all cases, isotretinoin was found to be a more effective therapy than its comparators. One study concluded that 0.5 mg/kg per day isotretinoin therapy for 16 weeks was significantly more effective than placebo, with a 97% overall decrease in number of cystic lesions at 41 months posttreatment [268]. Goldstein *et al.* [262] reported 1.0 mg/kg per day isotretinoin to be significantly more effective than 1.0 mg/kg per day etretinate after an 8-week course of therapy and at an 8-week posttreatment visit ( $P < 0.05$ ). Tetracycline performed equally well as isotretinoin by the end of a 16-week course of therapy in one RCT. However, at a 24-week visit (8-weeks posttreatment), isotretinoin therapy demonstrated a statistically significant decrease in the number of cystic lesions when compared with tetracycline therapy (85% overall reduction in number of lesions,  $P < 0.02$ ) [263]. Isotretinoin therapy was significantly more effective than dapsone therapy, as demonstrated by one 16-week RCT [270]. Isotretinoin therapy resulted in significantly fewer lesions on both face and trunk at 20, 28, and 36 weeks (4, 12, and 16 weeks posttreatment respectively). Isotretinoin therapy also achieved a better clinical result over minocycline in one 20-week RCT [273].

A recent RCT demonstrated that the addition of topical treatments, such as 1% clindamycin twice daily and 0.1% adapalene daily, to oral isotretinoin did not provide any additional efficacy in terms of clinical reduction in NILs and ILs in patients with severe nodulocystic acne [275].

Eleven RCTs compared various isotretinoin dosage regimens ranging from 0.1 mg/kg per day to 2.0 mg/kg per day [261,264, 267,269,272,274,276–278]. All doses studied resulted in a significantly decreased number of lesions. However, no dose-related clinical response could be detected among the doses tested. Only one trial [269] reported (somewhat anecdotally) that higher doses of

oral isotretinoin resulted in better clinical outcomes. However, no statistics were available to substantiate this claim. A recent RCT suggests that conventional daily dosing (1 mg/kg per day) for the first 8 weeks of treatment followed by alternating regimens (1 mg/kg every other day) or low-dose regimens (20 mg every other day) for another 8 weeks yields a similar reduction in total lesions compared with 16 weeks of daily dosing in patients with severe acne [276]. In addition, this “tapered” approach minimized the common side effects of oral isotretinoin.

Two similar RCTs support alternate dosing for patients with moderate acne. One study argued that both conventional (0.5–0.7 mg/kg per day) and low-dose (0.25–0.4 mg/kg per day) regimens have similar efficacy for patients with moderate acne [277], while another demonstrated that intermittent therapy has similar efficacy to conventional therapy in moderate acne [278]. Both of these studies, however, were not adequately powered to evaluate equivalence. Further investigation is needed to support alternative dosing for patients with moderate disease.

Several studies have also demonstrated significantly decreased SER [261,262,264,266,268,270,274], free fatty acid excretion [261], and bacterial [261,270] and yeast colonization with isotretinoin therapy. SER was shown to be significantly reduced in both a dose-dependent [264,266,267,272,274] and dose independent manner in several studies, but was also found to resume near-normal levels following termination of treatment at a rate that was inversely proportional to isotretinoin dosage [264,266,268,270]. In other words, higher doses of isotretinoin resulted in a more prolonged decrease in SER. One study reported a significant decrease in SER at 16 weeks posttreatment with 1.0 mg/kg per day ( $P < 0.0025$ ) [266]. The mechanism of decreased SER seems to be related to sebaceous gland atrophy, which begins to occur after 3 weeks of isotretinoin treatment [268,279,280]. Decreases in bacterial and yeast colonization were also noted in several studies [261,270]. One study noted a statistically significant, dose-independent decrease in anaerobic bacteria colonization after 16 weeks of treatment, but not of aerobic bacteria [261]. The same study also noted statistically significant, dose-independent decreases in *Pityrosporum* spp. at 16 weeks. Another study noted a statistically significant decrease in both aerobic and anaerobic bacteria colonization during treatment with isotretinoin [270]. It is hypothesized that the decreases in colonization are an indirect result of alterations in the microenvironment necessary for the survival of skin-surface microorganisms, rather than a direct antimicrobial effect [261,281,282].

Six RCTs included posttreatment evaluation in order to determine rates of long-term disease remission/relapse. Several studies noted a further decrease in acne severity during the posttreatment follow-up period [262–265,268,270]. Furthermore, one study noted that the degree of disease remission was significantly greater in patients who had been treated with higher doses of oral isotretinoin [265]. In one 20-week study, 40% of patients treated with 0.1 mg/kg per day needed to be retreated, while only 10% of patients who had been treated with 1.0 mg/kg per day needed retreatment [265]. Another study reported similar findings [268].

### Adverse effects

The teratogenic effect of isotretinoin is well documented [283]. None of the trials reported pregnancies, births, or birth defects. Most trials either excluded women with childbearing potential from the study or advised women to take adequate contraceptive measures.

Significant side effects of oral isotretinoin therapy were identified in all RCTs. In general, side effects were limited to the muco-

cutaneous membranes. Side effects were generally more severe with higher doses of isotretinoin therapy and generally resolved within 1 month of discontinuance of therapy. The most frequently cited side effects included cheilitis, xerosis, pruritus, facial dermatitis, epistaxis, and desquamation [261–270,272,273]. Hair loss [262,264,265,267,273], arthralgia [265,266,268,269,272], and decreased appetite [265,268,273] were reported in a small percentage of patients. Most patients chose to live with side effects in order to benefit from the effect of isotretinoin on the clearance of their acne. Very few patients discontinued therapy because it was unmanageable.

Several studies have investigated the relationship between depression/suicidal behavior and isotretinoin-treated acne patients [284–293]. However, these studies have not identified an association between depression/suicidal tendencies and isotretinoin therapy. Despite these negative findings, a consensus regarding the potential association has not been reached, primarily due to limitations (sample size, study design, etc.) of the studies. An important retrospective study from Sweden recently evaluated the potential link between oral isotretinoin, depression, and suicide. The study found that the risk of suicide attempts compared with the standard incidence of attempted suicide steadily increased 1 year prior to therapy, peaked at 6 months of therapy, and returned to baseline 3 years posttherapy. The rise in suicide attempts 6 months after treatment initiation cannot be solely linked to therapy because the risk was already gradually rising from 1 year previous [294].

Additionally, oral isotretinoin was found to cause a steady increase in serum triglyceride levels during treatment in several studies [263,269,272,273]. However, triglyceride levels were shown to decrease to normal levels after drug cessation [263–268,272,273]. Other laboratory findings included slight, transient elevations in serum protein [263,264,272], serum glutamic oxaloacetic transaminase [263,264,266,269,272], serum glutamic pyruvic transaminase [263,267,268], alkaline phosphatase [267], and serum cholesterol [269,270]. These elevations resolved either during or soon after cessation of treatment.

### Comment

In an effort to eliminate fetal exposure to isotretinoin in the USA, all isotretinoin distributors, distributing pharmacies, prescribers, and patients (both male and female) are required to register with the iPledge Program [295]. Female patients are required to report that two forms of contraception are being used simultaneously to their physician, as well as the results of a monthly pregnancy test. These protocols must be followed for 1 month prior to and 1 month following isotretinoin therapy. Male patients are not required to report contraceptive use, however, as there is not yet any evidence that isotretinoin therapy in males can cause teratogenic effects in fetuses. The iPledge Program was initiated in March 2006, and its efficacy in reducing fetal exposure to isotretinoin has yet to be fully determined [296].

### Implications for practice

Owing to the myriad potential side effects of oral isotretinoin, its use should ideally be reserved for the treatment of severe, recalcitrant acne. The many potential side effects of oral isotretinoin, including teratogenicity, mucocutaneous complaints, elevated lipids, elevated serum protein or liver transaminases, arthralgia, decreased appetite, and the possibility of depression with suicidal ideation, require close monitoring of the patient at regular intervals. The current recommendation suggests that the general practitioner



assesses for disturbances in mental health for 1 year after therapy cessation. Patient education should also be an integral part of isotretinoin therapy.

The teratogenicity of oral isotretinoin requires that extra care should be taken when prescribing the drug to female patients and demands that adequate methods of contraception should be insisted upon in order to prevent birth defects. Laboratory monitoring should include pregnancy screening for female patients, and periodic serum triglyceride, cholesterol, and liver function tests may be indicated for all patients during isotretinoin therapy.

Lastly, more prolonged course of therapy (16–20 weeks) with a relatively low dose of isotretinoin ( $\leq 1$  mg/kg per day) may provide an optimal balance between long term outcomes and side effects.

### Key points

- Antibacterial washes should be considered in the first-line management of mild acne and in the maintenance of individuals who have improved following other therapy. They should not be used routinely in conjunction with other therapies. There is no evidence to support the use of abrasives, which may further irritate already sensitized skin. Syndet bars are less irritant than soap for cleansing.
- Topical retinoids can be used in both noninflammatory and inflammatory acne and in conjunction with oral and topical antibiotics. The evidence suggests that adapalene is less irritant than other retinoids, though newer retinoid delivery systems produce less irritation.
- Azelaic acid is effective in mild to moderate acne and may be less irritant than topical retinoids, but has a slower onset of response.
- Benzoyl peroxide is an effective treatment in mild to moderate acne, but causes an initial sensitization that may persist in some individuals. Higher strength benzoyl peroxide is in general no more effective than at lower strength, but is associated with more irritation.
- Antibiotics are more effective against ILs than against NILs. There is no evidence to support a difference in efficacy between any of the agents, either oral or topical, although topical therapies are more cost effective.
- There is no good-quality evidence to support recommendations about either the dose or duration of antibiotic therapy; further research is needed.
- Benzoyl peroxide appears to have similar activity to antibiotics against ILs and greater activity against NILs, but causes local irritation. The evidence suggests that combined use of antibiotics with retinoids is more active than either agent alone, and whilst benzoyl peroxide combinations are more effective than antibiotics alone, the data against benzoyl peroxide alone are equivocal.
- Given concerns about the development of resistance, further research is urgently required to assess the efficacy of antibiotics relative to other agents and to provide data for an appropriate assessment of the risks and benefits associated with their continued use. Benzoyl peroxide should be used intermittently during extended antibiotic therapy to eliminate any resistant strains.
- Switching from an antibiotic regimen to a combination topical retinoid and benzoyl peroxide reduces antibiotic resistance.
- Oral isotretinoin should be reserved for severe, treatment resistant acne due to potentially serious adverse side effects, including teratogenicity.
- Patients on oral isotretinoin should be monitored for changes in lipids and liver enzymes.
- Patients requiring oral isotretinoin should be screened for depression before treatment is initiated and monitored for depression and suicidal ideation during therapy.

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Web tables referred to in this chapter are published on the book's website (<http://www.evidbasedderm.com>).



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## CHAPTER 20

# Papulopustular rosacea

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### Background

#### Definition

Papulopustular rosacea is a stage of rosacea in which papulopustules appear on the nose and cheeks, more rarely on the forehead and chin, and exceptionally on the neck and other body areas, such as the bare skull or the back. In some cases, papules show a granulomatous infiltrate, which is clinically identified from the yellowish color of the lesions and their duration (Figure 20.1). Lymphedematous rosacea is more rare and is characterized by chronic and persistent edema in the periocular and perinasal areas. The edema persists even when inflammation has abated and is probably linked to inflammatory damage to the regional lymphatic vessels. A hyperacute episode, in which most of the face is invaded by papulopustules (facial pyoderma), has also been described as rosacea fulminans.

Typically, rosacea is a multistage disease. The stages are the flushing stage, or transitory congestive redness; the erythrosis stage, of persistent telangiectatic redness; the papulopustular stage; and the phyma stage. Only a minority of patients with the first two stages of the disease progress to the papulopustular stage and fewer to the phyma stage.

Although ocular symptoms are recorded in as many as 20.8% of cases, the introduction of a stage named “ocular rosacea” is not acceptable. Ocular rosacea goes through most of the stages mentioned above, including a congestive stage (blepharo-conjunctivitis) and a papulopustular stage (sties and chalazas).

#### Incidence/prevalence

Rosacea is a very common disease. In the USA, it is the fifth most frequently diagnosed skin condition after acne, atopic dermatitis, psoriasis, and actinic keratoses. It affects 10% of the general population in Sweden.

A recent study in the UK revealed that the overall incidence of rosacea is 1.65 per 1000 persons/year, with a definite prevalence of women (61.5%). In 80% of cases, rosacea is diagnosed after the age of 30 years [1]. However, this depends on the stage in which the condition is diagnosed. In 1979 in Italy, the flushing stage was in fact found to occur already in the second decade of life and eryth-

rosis at the mean age of 34 years. Phymas develop later (mean age 66 years).

#### Etiology/risk

The etiopathogenesis of papulopustular rosacea is controversial. Heredity is important. It has been shown that 20% of the children with steroid rosacea had at least one close blood relative with rosacea. Fair complexion, blond hair, and green/blue eyes are characteristics of patients with rosacea. Southern, darker complexions, therefore, have a lower incidence. In fact, only about 0.1% of colored people are affected by rosacea, as reported by an old American observation.

Also unclear is why a patient proceeds from stages that are mainly functional to stages that are inflammatory. Both cell-mediated and humoral arms of immunity are certainly involved. Antibodies directed against collagen VII, the pericapillary elastotic tissue, and the *Demodex folliculorum* mites have been detected. However, the production of antibodies may be a secondary event, or the elastotic tissue and *D. folliculorum* may simply represent structures on which antibodies accumulate spontaneously (“beach effect”). In addition, *Helicobacter pylori*, a Gram-negative bacterium, may play a role. Opinions diverge on its association with rosacea, but drugs that eradicate *H. pylori* were used to treat papulopustular rosacea efficaciously long before the discovery of the bacterium.

Recently, attention has been paid to cathelicidin processing, which would be disturbed in rosacea resulting in the production of peptide fragments responsible for inflammation and telangiectases. Cathelicidin is strongly increased in rosacea lesional skin, and the injection into the skin of mice of the peptide fragments found in skin of rosacea patients leads to a rosacea-like disease. In particular, the role of cathelicidin LL-37 has been studied. Its expression in human keratinocytes is regulated by the vitamin D pathway, and this could explain why rosacea occurs in the sun-exposed sites. Other external stimuli, like infections, injuries, and disruption of the permeability barrier, have been found to trigger the induction of cathelicidin synthesis in keratinocytes. Doxycycline efficacy has been explained by its capacity to prevent cathelicidin activation [2,3].

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**Figure 20.1** A patient with rosacea (a) before and (b) after treatment. (Figures provided by Andrew Herxheimer.)

### Prognosis

No long-term prognostic studies are available.

### Aims

The aims of treatment are to suppress the symptoms and to maintain such suppression over time.

### Outcomes

The following outcome measures are used: state of lesions over time; use of routine treatments; duration of remission; patient satisfaction; disease-related quality of life; adverse effects of treatments, and clinical activity scores.

### Methods

One Cochrane review was published in 2005 and included 29 studies, one systematic review, and one partial review [4]. A new Cochrane review was published in 2011 and included 58 studies [5]. None of the patient-reported outcome assessment tools met the recommended criteria based on the quality “checklist.” In six of the studies the self-assessments were made by way of questionnaires of unsupported validity, and in general the quality of the evidence was considered only low to moderate [6].

## Questions

### What are the effects of systemic treatments?

#### Tetracycline

##### Efficacy

In the Cochrane review on cutaneous and ocular rosacea [4], data pooled from three studies of oral tetracyclines versus placebo, including 152 participants, showed that tetracycline was effective (odds ratio [OR], 6.06; 95% confidence interval [CI], 2.96–12.42).

The systematic review of ocular rosacea examined 11 papers, only three of which were randomized controlled trials (RCTs). The proportion of patients with improvement ranged from 20% to 100%. It was concluded that there is a moderate benefit with oxytetracycline, whilst the efficacy of tetracyclines and doxycycline could not be established [7].

##### Drawbacks

Diarrhea at 750 mg/day was reported in one study and in 25% of cases treated with 40 mg/day [7].

##### Comment

In one RCT, a very minor placebo effect contrasted with all the other trials, in which there was a very marked placebo effect.

#### Doxycycline

Doxycycline is perhaps the most popular medication for papulopustular rosacea, but the Cochrane review did not identify any RCTs on doxycycline at traditional doses.

##### Efficacy

In one controlled clinical trial (CCT), 17 patients received doxycycline 200 mg/day for 4 weeks and then 100 mg/day for another month. The lesions cleared in 90% of patients in 8 weeks. Comparison with clarithromycin favored the latter [8]. An anecdotal report of two cases stated that 100 mg/day for 9 weeks and 50 mg/day for 1 month were sufficient to clear the lesions [9].

In more recent years, doxycycline has been used at a lower dose (40 mg/day), allegedly providing an anti-inflammatory activity. It proved more effective than topical metronidazole [10,11] or placebo [12] in RCTs. A physician-based assessment revealed no statistical difference in efficacy between the 40 and 100 mg doses [13]. In a recent large, open-label, multicenter, community-based study,

modified-release doxycycline capsules (30 mg immediate-release and 10 mg delayed-release beads) were used once daily for up to 12 weeks in 1421 patients with papulopustular rosacea. Significant improvements in severity rating and erythema were observed in more than 70% of patients [14].

### **Drawbacks**

Side effects (primarily mild or moderate gastrointestinal events) were complained of in about 10% of cases treated with 40 mg/day [14].

### **Comment**

Doxycycline is a photosensitizing agent in fewer than 1% of patients, but this characteristic should not be neglected in rosacea patients, who are usually fairly skinned. Bacterial resistance to subantimicrobial-dose doxycycline might arise after such low-dose treatment. In addition, although well designed, the recent RCTs on 40 mg doxycycline did not address the patients' views [15].

### **Ampicillin**

Ampicillin is rarely used.

### **Efficacy**

In the only RCT, 17 patients were treated with ampicillin 750 mg/day for 6 weeks. There was a 55% improvement in the lesions. When the results were assessed by a scoring system, tetracycline and ampicillin proved significantly better than placebo; tetracycline was better than ampicillin, but the difference did not quite reach the 5% significance level [16].

### **Drawbacks**

Two patients developed diarrhea within a few days and withdrew from the study.

### **Comment**

The benefit/harm ratio appears to be low.

### **Clarithromycin**

No systematic reviews and no RCTs were found.

### **Efficacy**

In the only CCT, 23 patients received clarithromycin 500 mg/day for 1 month and then 250 mg/day for a further month. Ninety percent of the lesions cleared in 8 weeks; the comparison with doxycycline was in favor of clarithromycin [8].

### **Drawbacks**

Clarithromycin was significantly better tolerated than doxycycline.

### **Comment**

Clarithromycin is almost four times more expensive than doxycycline.

### **Azithromycin**

There are no systematic reviews or RCTs.

### **Efficacy**

One randomized open clinical trial found azithromycin as equally effective as doxycycline, but the standard deviations were large and the data were skewed [17]. An uncontrolled study reported that

clearing occurred in 9 of 10 patients treated with azithromycin 500 mg/day for 4 weeks followed by 250 mg/day for 3 months [18]. Another uncontrolled study reported that 10 adults treated with azithromycin (250 mg three times/week) had moderate or marked improvement within 4 weeks [19]. Another open-labeled study included 18 patients who received azithromycin for 12 weeks, in decreasing doses. In the 14 patients who completed the study, the total scores significantly decreased by 75%, and the improvement continued during the month after treatment [20].

### **Drawbacks**

Nausea in one patient resolved without the treatment having to be interrupted.

### **Comment**

A once-daily pulse-dosing regimen may improve compliance.

### **Metronidazole**

Oral metronidazole appears to be highly effective in papulopustular rosacea.

### **Efficacy**

In the first of two RCTs, 29 patients received metronidazole 400 mg/day for 6 weeks. The benefit was significantly superior to placebo [21]. In the second trial, 40 patients received 400 mg/day for 12 weeks. The improvement was similar to that obtained with oxytetracycline [22]. An uncontrolled trial treated 59 patients with 500 mg/day for no more than 6 months, obtaining 90% success rate [23]. Further trials have been published in German [24].

### **Drawbacks**

Headache and furred tongue have been noted occasionally.

### **Comment**

Metronidazole is reported as having a disulfiram-like effect. This must be a very rare side effect, as in my (AR) large personal experience I have never come across it.

### **Eradication of *Helicobacter pylori***

It is still a matter of controversy whether *H. pylori* is involved in the pathogenesis of rosacea. However, eradication of *H. pylori* results in clearing papulopustular rosacea.

### **Efficacy**

Only one RCT was found, in which 44 patients were treated with omeprazole 40 mg/day plus clarithromycin 1500 mg/day for 2 weeks. Skin lesions cleared in almost all patients, but there were no differences from the untreated controls [25]. In one CCT, 37 patients received omeprazole 40 mg/day for 1 month, plus clarithromycin 100 mg/day, plus metronidazole 2000 mg/day for 2 weeks. At the 12th week, 76% of the patients experienced improvement, compared with no improvement in the 26 untreated patients [26]. In another CCT, 53 patients received omeprazole 20 mg/day, clarithromycin 1 g/day, and metronidazole 1 g/day for 1 week. Ninety-six percent cleared in 2–4 weeks [27]. In a controlled non-randomized study, 13 patients improved on bismuth 1200 mg/day, amoxicillin 500 mg/day, and metronidazole 1.5 g/day [28].

### **Drawbacks**

Surprisingly, no information is provided regarding any side effects of such a complex therapy.

**Comment**

The Cochrane systematic review regarded the data reported for clarithromycin and omeprazole as unusable [5]. The results, however, are homogeneously in favor of the efficacy of the eradication of *H. pylori*, with the exception of the RCT. It is very difficult to believe, however, that the placebo-treated patients improved as much as those who received the eradication therapy. It has to be noted, however, that the RCT did not use metronidazole [25].

**Isotretinoin**

Isotretinoin is a drug for very severe cases, such as pyoderma faciale.

**Efficacy**

No systematic reviews were found, but there was one RCT in which 20 patients received isotretinoin 10 mg/day for 4 months. They improved significantly [29]. In an uncontrolled study, 22 patients received isotretinoin 10 mg/day for 4 months. They improved by 50% in 9 weeks [30]. Two anecdotal reports described clearance in 3–6 months [31,32].

**Drawbacks**

Most patients experienced dry lips and facial xerosis, and 25% a mild to moderate increase in serum triglyceride levels.

**Comment**

Long-term side effects have not been reported.

**Octreotide****Efficacy**

In an anecdotal observation, the lesions cleared in three of four patients [33].

**Zinc sulfate**

We found two RCTs dealing with zinc sulfate.

**Efficacy**

In one RCT [34], zinc sulfate 100 mg three times a day improved significantly facial rosacea in 19 patients. Improvement started directly after the first month of therapy. After shifting to placebo treatment, rosacea relapsed gradually in the fifth month, but its severity remained significantly lower than before therapy. In the second RCT [35], 220 mg of zinc sulfate was given twice a day for 3 months to 44 patients with moderately severe rosacea. Rosacea improved in both treated and placebo groups. No differences were noted.

**Drawbacks**

Mild gastric upset was noted in 12% of cases of the first RCT.

**Comment**

Additional studies are needed.

**What are the effects of topical drugs?**

Topical drugs are less likely to cause systemic adverse effects than systemically administered drugs, and compliance may be better. It should be noted, however, that the rosacea skin is extremely reactive to external agents, including cosmetics, and that skin mites, like *D. folliculorum*, are lipophilic organisms that may be fed by oily medications. According to the Cochrane study [6], most of the

studies with topical treatments other than antibiotics are at high risk of bias and had skewed or unusable data.

The drug that has been most widely tested is metronidazole.

**Metronidazole**

Metronidazole, formulated as either a 1% cream or a 0.75% gel, has proved effective in papulopustular rosacea [36].

**Efficacy**

The Cochrane review [4] found that topical metronidazole is more effective than placebo. Although most of the studies did not specifically address participants' satisfaction with treatment and were largely physician assessed, the lesion counts were in fact reduced. Most studies used 0.75% metronidazole applied twice a day. Different formulations, such as gel, cream, and lotion, are deemed to be equivalent. The treatment period varied from 8 to 9 weeks in most trials, but was 6 months in one study. The Cochrane review documented improvement over placebo in both "self-assessment by the patient" (three studies; OR, 5.96; 95% CI, 2.95–12.06) and physician global evaluation (three studies; OR, 7.01; 95% CI, 3.56–13.81). The data on continuous outcome measures, such as the number of lesions, could not be pooled because of the lack of relevant information, such as standard deviation.

However, these data supported the positive treatment effect. In an RCT, 88 patients, previously treated successfully with oral tetracycline and topical metronidazole, were treated with either 0.76% metronidazole gel or a vehicle. Relapses after 6 months of treatment were significantly fewer (23%) with metronidazole than with the vehicle (42%) [37].

Two studies compared metronidazole with oral tetracyclines [38,39]. Neither study could demonstrate a statistical difference between the drugs analyzed. However, the studies were too small ( $n = 25$  and  $n = 26$ ) to document a clinically significant difference. Two studies compared topical metronidazole with topical azelaic acid. One study ( $n = 251$ ) [40] was not able to document any difference (OR, 1.32; 95% CI, 0.79–2.21) in patient self-assessment, but both the physician assessment and count of inflammatory lesions were in favor of azelaic acid (inflammatory lesions 12.9 vs 10.7;  $P = 0.003$ ). The other study ( $n = 40$ ) [41] involved a within-patient comparison, and again found that azelaic acid was slightly superior to metronidazole. The clinical significance of the difference documented is difficult to define. In one study in which topical metronidazole was compared with permethrin ( $n = 63$ ) [42], no difference was documented in the erythema score or papule count, but there was a reduced number of pustular lesions in the permethrin group.

**Drawbacks**

Side effects occurred in 2–4% of patients and included dryness, burning, and stinging. One paper reported that both the metronidazole gel and its excipient seemed to be poorly tolerated [43].

**Comment**

The majority of papers were RCTs (some even multicenter), mostly comparing the drug with a vehicle, but were sponsored by manufacturers.

**Azelaic acid**

Azelaic acid has been found to be effective in rosacea [44]. The Cochrane review found four RCTs comparing azelaic acid with placebo and one RCT comparing the drug with topical metronidazole.

**Efficacy**

Both 15% and 20% azelaic acid concentrations have been used in placebo-controlled RCTs, and the treatment period ranged from 12 to 13 weeks. It was estimated that about five patients had to be treated to obtain one experiencing complete remission or marked improvement (number needed to treat, 5; 95% CI, 4–7) [40]. Two RCTs reported comparisons with topical metronidazole (see above) [40,41]. Azelaic acid 15% gel proved to be more irritant than metronidazole 0.75% gel in a series of 33 patients [45].

**Drawbacks**

Burning and stinging have been noted.

**Comment**

The quality of the studies was generally poor [44].

**Sulfur**

Sulfur appears to be effective in rosacea. Two RCTs were found.

**Efficacy**

In the first RCT [46], 20 patients were treated for 1 month with a 10% sulfur cream plus placebo tablets and compared with 20 patients treated with lymecycline 150 mg/day plus placebo cream. Ninety-two percent of the lesions cleared with both treatments. In the second study, a total of 94 patients were treated with a combination of 10% sodium sulfacetamide and 5% sulfur in a lotion for 8 weeks. Inflammatory lesions decreased by 78%, in comparison with 36% in the vehicle group [47].

**Drawbacks**

Reactions at the application site decreased in frequency over time.

**Permethrin****Efficacy**

An RCT has been carried out, including 63 patients randomly assigned to permethrin 5% gel, metronidazole 0.75% gel, or placebo. Permethrin was as effective as metronidazole gel and significantly superior to placebo (see above) [42].

**Tretinoin/isotretinoin**

Isotretinoin may be effective in rosacea.

**Efficacy**

In one small RCT, six patients were treated with 0.025% tretinoin cream for 16 weeks. Lesion counts decreased by 42%. No additional benefit was noted if the patients were also treated with oral isotretinoin [29]. In an uncontrolled small trial, four patients were treated with 0.2% isotretinoin cream for 16 days. Inflammatory lesions responded better than noninflammatory lesions [48].

**Drawbacks**

No side effects were noted.

**Comment**

It is well known that isotretinoin irritates normal skin, but surprisingly it does not irritate the sensitive rosacea skin.

**Clindamycin**

Two RCT have been published. In the first one, 43 patients were randomly assigned to treatment with either 1% clindamycin phosphate lotion for 12 weeks or tetracycline 1000 mg for 3 weeks and then 500 mg for 9 weeks. All inflammatory lesions decreased signifi-

cantly (by about 60%) in the clindamycin arm, while only papules and nodules decreased significantly in the tetracycline arm [49].

In the second RCT, 70 patients with moderate to severe papulopustular rosacea were treated with a combination topical clindamycin phosphate 1.2% and tretinoin 0.025% for 3 months. The combination may improve the telangiectatic component of rosacea rather than papulopustules [50].

**Drawbacks**

Facial scaling was noted in the second RCT, though it did not lead to discontinuation.

**Benzoyl peroxide****Efficacy**

In the only CCT, patients were treated with 5% benzoyl peroxide acetone gel for 1 month and with 10% gel for a further month. Benzoyl peroxide was superior to placebo [51].

**Drawbacks**

Twenty-three percent of the patients treated with benzoyl peroxide dropped out of the study.

**Calcineurin inhibitors**

In one RCT [52], topical 1% pimecrolimus was found not to be better than the vehicle. In another open-label study [53], 26 patients were treated with 1% pimecrolimus cream for 1 month. Rosacea clinical scores were significantly reduced from  $9.65 \pm 1.79$  at baseline to  $7.27 \pm 2.11$  at the end of treatment ( $P < 0.05$ ). The side effects were mostly transient local irritations. In a randomized, open-label study, 48 patients were treated with either pimecrolimus 1% cream or metronidazole 1% cream for 12 weeks [54]. Both treatments were very effective without any significant differences. There is also an anecdotal report of a successful treatment of granulomatous rosacea [55]. Tacrolimus has been tried only in telangiectatic rosacea with good results in 60% after 6 weeks [56].

**Comment**

Rosacea-like and granulomatous dermatitis has been reported to occur in patients with the continuous use of topical calcineurin inhibitors [57,58].

**Laser and/or light-based treatments**

They were directed essentially on erythematotelangiectatic rosacea and cannot be analyzed here. "Acne rosacea" was less responsive [59].

**Key points**

- Only a few RCTs have been conducted on systemic agents. In particular, no RCTs have tested doxycycline, clarithromycin, or azithromycin.
- Many RCTs have been performed with topical drugs. In particular, metronidazole has been extensively and thoroughly studied.
- Almost all of the drugs examined were found to be effective, and this is surprising given the profound chemical diversity of the drugs used and the poor explanation provided for their activity.
- Side effects were surprisingly minimal, even for drugs such as tretinoin and benzoyl peroxide which are well-known irritants.
- In many studies, a high rate of response to placebos was observed.
- The large majority of RCTs have been directly supported by the manufacturer. The obvious conflict of interest cannot be neglected in evaluating the results.



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## CHAPTER 21

# Perioral dermatitis

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## Background

### Definition

Perioral dermatitis is a common inflammatory and chronic facial dermatitis symmetrically involving the area delimited by the alae of the nose and the chin. It can also involve periorbital and perinasal areas. For this reason, perioral dermatitis is also known as periorificial dermatitis.

It is characterized by an eruption of 1–2 mm erythematous papules, papulopustules, or papulovesicles (Figure 21.1). Acneiform eruption may also be present. Frequently the eruption occurs with diffuse erythema and scaling and often spares a narrow zone around the vermillion border.

An associated sensation of burning is common, while itching is not usually present [1,2].

### Incidence/prevalence

The exact incidence and prevalence are unknown. Perioral dermatitis in 90% of the cases affects women in the 16–45 age group. The incidence in men is increasing. The condition is seldom seen in children, particularly from age 7 months to 13 years [1,2].

### Etiology

The etiology of perioral dermatitis is unknown. The possible causative factors include infection, such as *Candida* or *Demodex*, use of potent topical steroids, cosmetics, fluoride toothpastes, physical factors (UV, heat, wind), hormonal or emotional factors, the use of oral contraceptives, and the presence of gastrointestinal disturbance [1].

### Prognosis

Following discontinuation of the offending etiologic factor, and with the appropriate treatment, perioral dermatitis generally regresses in a few weeks. Perioral dermatitis is therefore associated with an excellent prognosis.

### Aims of treatment

When treating patients with perioral dermatitis, physicians aim to achieve clinical clearance in a time as short as possible and prevent recurrence, while minimizing the adverse effects of treatment.

## Outcomes

The standard outcomes of treatment include clinical clearance, recurrence rates, and adverse effects of treatment.

To assess clinical severity of perioral dermatitis, a score, the perioral dermatitis severity index (PODSI), was developed in 2005. This index represents the sum of individual scores for erythema, papules and scaling using a scale from 0 (none) to 3 (severe), including intermediate values (0.5, 1.5, and 2.5) and resulting in a total score from 0 to 9 [3].

## Methods of search

To identify studies on the treatment of perioral dermatitis, Medline (until 2012) was checked for publications in English. Since only a few randomized controlled trials (RCTs) were identified, publications including case series were included. Evidence was graded using the level of evidence scale system reported by Hall and Reichenberg [2]. All evidence found in the literature is presented.

## Questions

### What are the effects of “zero therapy”?

#### Level of evidence: A

“Zero therapy” means avoiding the use of cosmetics and corticosteroids.

The subjects who made up the control group of four randomized clinical trials and who were treated with an oral placebo or a vehicle cream were counseled to avoid using topical corticosteroids and cosmetics. Most of these patients cleared within 2–3 months, with significant improvement generally seen in the first 4 weeks [4–7].

#### Comment

In four studies, perioral dermatitis, in patients of the control groups that did not receive an active treatment, resolved within 2–3 months after topical corticosteroids and cosmetic suspension.

### What are the effects of metronidazole?

#### Metronidazole 1% cream/metronidazole 0.75% gel

#### Level of evidence: A

We found no studies comparing metronidazole 1% cream with placebo.



**Figure 21.1** A patient with perioral dermatitis.

There is only one prospective, double-blind, double-dummy, multicenter RCT that compares metronidazole 1% cream with oral tetracycline in the treatment of perioral dermatitis [8].

As far as metronidazole 0.75% gel is concerned, no systematic reviews or RCTs have been found.

#### **Efficacy**

The multicenter RCT was conducted in 109 patients randomly assigned to receive either 1% metronidazole cream plus placebo tablets twice daily, or placebo cream and tetracycline tablets (250 mg twice daily) [8].

In the metronidazole group, the median number of papules was reduced to 33% of the original number after 4 weeks and to 8% after 8 weeks. The median number of papule reductions in patients treated with tetracycline was reduced to 4% after 4 weeks, and 0% at 8 weeks. Tetracycline was significantly more effective in reducing the number of papules after 4 and 8 weeks of treatment ( $P < 0.01$ ). No significant differences were noted in any of the other categories evaluated, which included erythema and patient and physician assessments.

#### **Drawbacks**

Seven patients out of 54 in the metronidazole group and nine out of 54 patients in the tetracycline group complained of adverse effects, the most common of which included abdominal discomfort, pruritus, and dryness of the face.

#### **Level of evidence: C**

A retrospective study evaluated the efficacy of topical metronidazole used alone or in combination with other medications such as oral erythromycin in 41 children or adolescents from 6 months to 18 years of age [9].

In this group of patients, perioral dermatitis was reported to last from 1 to 24 weeks (7 weeks on average). In only one patient did the facial rash persist. In contrast to patients who received no treat-

ment or other treatments such as topical calcineurin inhibitors, sulfacetamide, hydrocortisone, and antifungal agents, those patients treated with topical metronidazole, oral erythromycin, or both were associated with absence of lesions at the follow-up visits. No adverse events were reported.

Moreover, in a retrospective study on 15 patients affected by demodicosis, skin lesions rapidly resolved after systemic metronidazole and/or 0.75% gel. In five patients the condition manifested as a perioral dermatitis-like rash [10].

#### **Level of evidence: D**

A case series including seven children using metronidazole 1% cream twice daily showed slow but significant improvement after 4–6 weeks and resolution after 3–6 months [11].

#### **Level of evidence: E**

Eleven out of 17 cases of perioral dermatitis in children between the ages of 9 months and 9 years were treated with monotherapy consisting of metronidazole gel 0.75% either once or twice daily. The remaining patients were given combination therapy of metronidazole gel with topical corticosteroids or erythromycin (topical or oral). All patients improved within 8 weeks of therapy. Fourteen patients who were followed up remained lesion-free for up to 16 months. No adverse reactions were reported [12,13].

#### **Comment**

Only one RCT comparing the efficacy of metronidazole 1% cream with that of oral tetracycline is available. It shows that tetracycline is more effective than metronidazole 1% cream in reducing the number of the papules. Other available data are related to case series and retrospective studies in children or adolescents. In particular, no studies on adults with perioral dermatitis using metronidazole 0.75% gel were found.

Patients improve with metronidazole, but there are no data to quantify the entity and the rapidity of improvement in comparison with placebo.

### **What are the effects of oral tetracyclines?**

#### **Oral tetracyclines**

##### **Level of evidence: A**

Three randomized clinical trials and many cases series have studied the efficacy of oral tetracyclines, as reported in a recent review [2] of perioral dermatitis therapy [4,5,8,14].

#### **Efficacy**

Data show that the results with tetracycline 250–500 mg orally twice daily for 20–60 days are superior to oral placebo and to metronidazole 1% cream twice daily and either better or equal to topical erythromycin. Most of the papules resolve within the first month of therapy, and complete resolution is achieved in about 2 months [4,5,8].

In only one trial with 50 patients was the treatment with oral tetracycline found to be no more efficacious than “zero therapy” [8].

Weber, in a series of about 700 patients found that, in 2% of the patients who failed to respond to topical erythromycin ointment, oral tetracycline could effectively bring resolution of papules in 3–5 weeks [14].

#### **Drawbacks**

No adverse events were reported.

**Comment**

These three RCTs confirm that tetracycline is an effective first-line treatment for perioral dermatitis and that it is effective also in those who failed other previous treatments.

**Level of evidence: D**

Only low-level evidence and cases series support the use of minocycline, doxycycline, and oxytetracycline [2].

None of the reports were placebo controlled, and many used multiple oral and topical agents in combination. For this reason, it is very difficult to compare the results of different cases.

Furthermore, with the lack of high-quality evidence available, it is difficult to determine the efficacy of these tetracyclines in the treatment of perioral dermatitis.

**What are the effects of topical antibiotics?****Topical tetracycline****Level of evidence: C**

The effects of topical tetracycline were evaluated in the treatment of perioral dermatitis. As the source of this topical preparation was not disclosed, the dose, potency, and efficacy of this type of tetracycline preparation must be questioned.

**Efficacy**

A case series of 30 patients (26 females, 4 males) with clinically typical perioral dermatitis has been reported [15]. Patients were asked to apply topical tetracycline twice daily to all affected areas after gently washing the face. No other treatment was allowed. Twenty-four patients (80%) experienced complete clearing of their condition in 5–28 days; three patients (10%) were at least 50% clear within 28 days; and three patients (10%) discontinued the medication. All patients whose condition cleared were able to maintain clearing with the topical product used on an as-needed basis.

**Drawbacks**

Two patients discontinued therapy due to stinging, and one patient discontinued because of worsening of the dermatitis.

**Comment**

We found no RCTs on the treatment of perioral dermatitis with topical tetracycline.

Based on this case series, topical tetracycline twice daily for 1–4 weeks results in improvement or “clearance” in most of the cases within 28 days.

**Topical erythromycin****Level of evidence: A**

Cases series and a single randomized placebo-controlled trial support the use of topical erythromycin for perioral dermatitis.

**Efficacy**

In the single randomized placebo-controlled trial, 33 patients were treated with topical erythromycin 2% emulsion twice daily, 35 with oral tetracycline, and 33 with placebo. Topical erythromycin was shown to be significantly better than placebo in reducing papules, but at day 20 tetracycline was shown to be superior ( $P = 0.07$ ). Average time to papules clearance was 7 weeks in the topical erythromycin group [5].

In a cases series of 665 patients, all papules disappeared in 79% within 3–5 weeks of treatment with erythromycin 2% ointment [14].

Six patients in a case series were treated with 1.5% erythromycin topical solution twice daily in combination with hydrocortisone valerate cream [16]. Topical 1.5% erythromycin was effective in the treatment of perioral dermatitis, with a mean treatment duration of 4.5 weeks.

**Drawbacks**

Fourteen patients referred to an unbearable burning [14].

**Comment**

One RCT found that erythromycin 2% ointment twice daily for 4–8 weeks results in clearance of papules within 3–5 weeks, showing a better efficacy than placebo [5,14]. Total clearance of erythema may need several more weeks.

**What are the effects of nonfluorinated corticosteroids?****Hydrocortisone butyrate****Level of evidence: D**

Insufficient evidence has been found on the effects of nonfluorinated corticosteroids in patients with perioral dermatitis. One study, a split-face randomized trial of hydrocortisone butyrate versus 1% hydrocortisone alcohol cream in the treatment of rosacea, atopic dermatitis, and perioral dermatitis, is available.

**Efficacy**

In the double-blind, split-face, randomized trial, patients with perioral dermatitis (eight patients), rosacea (18 patients), or atopic dermatitis (two patients) were randomly treated on one side of their face with hydrocortisone alcohol 1% cream and the other side with 0.1% hydrocortisone butyrate [17]. Only patients with severe disease were selected. The participants were instructed to apply the creams twice daily to the appropriate side of the face. Six of the eight patients with perioral dermatitis also received oxytetracycline 250 mg twice daily. The patients were reexamined weekly by the same physician until more improvement was noted on one side of the face in comparison with the opposite side. If no difference was detected, treatment continued for up to 3 months. In addition, the patients were reexamined 1 week after treatment was withdrawn to determine whether any rebound occurred. Two patients with perioral dermatitis achieved better results with hydrocortisone alcohol 1% cream (mean duration of therapy 3.5 weeks, range 3–4 weeks), four patients improved more with hydrocortisone butyrate (mean duration: 3–5 weeks, range 2–5 weeks), and two patients found both treatments equally effective.

**Drawbacks**

Two patients with perioral dermatitis showed a moderate rebound of the eruption after withdrawal of topical treatment, in each case on the hydroxybutyrate-treated side of the face.

**Comment**

In view of the study design and the small numbers of patients, it is difficult to draw conclusions.

**Other treatment modalities****Photodynamic therapy with 5-aminolevulinic acid****Level of evidence: C**

No placebo-controlled RCTs were found. The only evidence for the treatment of perioral dermatitis with 5-aminolevulinic acid (ALA)–photodynamic therapy (PDT) was one prospective, split-face trial

performed without randomization (in most cases, the side with the highest number of lesions was treated with ALA-PDT) [18]. The concentration of the comparator, clindamycin gel applied once daily, was not disclosed. In addition, the results were reported in terms of the per-protocol population ( $n = 14$ ) instead of the intention-to-treat population ( $n = 21$ ).

### Efficacy

In a split-face study including 21 patients (19 women and 2 men), perioral dermatitis was treated with unoccluded ALA followed by treatment with 410 nm blue light for 8 min on one side of the face and with topical clindamycin phosphate gel applied daily on the other side [17]. The patients had to have at least three facial lesions (as identified by clinical observation) on each side of the face. Patients who completed the study received an average of three weekly PDTs (range 1–4) each over 1 month. The responses were considered complete if no lesion was seen at the treatment site. Patient-graded satisfaction was reported using a five-point scale (where 5 was complete satisfaction) [18].

Fourteen patients (66.7%) completed the study, all of whom received four PDTs to achieve complete or nearly complete clearance by either treatment modality. Seven patients did not complete the study owing to skin photosensitivity irritation brought on by a failure to avoid sun exposure for the recommended 48 h after treatment. The mean post-treatment lesion counts – 1.4 for ALA-PDT and 2.3 for clindamycin gel – did not differ significantly ( $P = 0.1140$ ). However, the mean lesion counts after treatment were significantly less than the mean lesion count at baseline for both ALA-PDT ( $P < 0.0001$ ) and clindamycin gel ( $P = 0.0001$ ). The sides treated with ALA-PDT achieved a significantly better mean clearance ( $P = 0.0227$ ) in comparison with the clindamycin side (clearance of 92.1% with ALA-PDT and clearance of 80.9% with clindamycin). In nine of the 14 patients, the greater level of clearance was on the ALA-PDT side. The mean patient satisfaction level for the side treated with ALA-PDT was 4.4; the level of satisfaction for the clindamycin gel side was not reported [18].

### Drawbacks

Mild postinflammatory hyperpigmentation occurred in three patients in the study. In addition, skin photosensitivity irritation reactions can occur in those who do not avoid sun exposure for 48 h after treatment [18].

### Comment

In the absence of large-scale, well-designed RCTs, it is difficult to fully assess the impact of ALA-PDT in the treatment of perioral dermatitis. In addition, this seems to be the only published trial incorporating topical clindamycin into a treatment regimen for

perioral dermatitis; but again, it is difficult to draw conclusions concerning this treatment modality owing to the small number of patients and the overall study design.

### Azelaic acid

#### Level of evidence: C

There are no placebo-controlled RCTs involving azelaic acid in the treatment of perioral dermatitis. Only two open clinical trials investigating the efficacy and tolerability of 20% azelaic acid cream in the treatment of perioral dermatitis in a total of 20 patients, 10 adults and 10 children, were found [19,20].

### Efficacy

Ten adult patients with perioral dermatitis were treated with 20% azelaic acid cream applied twice daily (overall duration of use not specified). All patients responded to treatment within 2–3 weeks, with clearing of all lesions within 2–6 weeks. There were no reported recurrences of the disease after 4–10 months of follow-up [19].

Ten children (from 3 to 12 years of age) applied 20% azelaic acid cream twice daily until complete resolution of the perioral dermatitis, which occurred after 4–8 weeks. No recurrence was observed in a follow-up period of 2–8 months [20].

### Drawbacks

Two of the 10 adult patients reported erythema, itching, and dryness of the face. These were observed mainly in the initial 2 weeks of treatment [19].

Six of the 10 children complained of burning, erythema, or scaling immediately after topical application, above all during the first 2 weeks of treatment [20].

### Comment

There is a definite need for placebo-controlled and comparative RCTs before any comment can be made on the effectiveness of azelaic acid in the treatment of perioral dermatitis.

### Topical pimecrolimus

#### Level of evidence: A

Two randomized, double-blind vehicle-controlled studies, one with 124 patients and one with 40 patients, have been published [6,7].

### Efficacy

Data regarding the efficacy of a 4-week treatment with pimecrolimus cream 1% are reported in the Table 21.1.

In the study including 40 patients, 20 of them received pimecrolimus cream 1% and 20 a vehicle cream. The PODSI reduced from  $4.5 \pm 1.3$  to  $1.6 \pm 1.8$  in the pimecrolimus group and from  $4.6 \pm 1.1$  to  $2.6 \pm 1.5$  in the placebo group. The time of response

**Table 21.1** The results of RCTs evaluating the use of pimecrolimus cream 1% in perioral dermatitis.

	No. patients	PODSI				Time of response (weeks) (decrease PODSI $\geq 50\%$ )		Patients with recurrence (increase PODSI $\geq 50\%$ )	
		Pimecrolimus		Vehicle		Pimecrolimus	Vehicle	Pimecrolimus	Vehicle
		Before	After	Before	After				
Oppel <i>et al.</i> [7]	40	4.5 $\pm$ 1.3	1.6 $\pm$ 1.8	4.6 $\pm$ 1.1	2.6 $\pm$ 1.5	1	4	Not assessed	
Schwarz <i>et al.</i> [6]	124	5.2	2.1	5.2	2.4	1 (40% patients) 4 (65% patients)	1 (11%) 4 (60%)	10	6



was more rapid in the pimecrolimus group. In this study, follow-up after treatment lasted 4 weeks [7]. The rate of relapse was not evaluated.

In the study including 124 patients, 60 were treated with pimecrolimus cream 1% and 64 with a vehicle cream. A total of 112 patients completed the treatment phase. The PODSI reduced from 5.2 to 2.1 in the pimecrolimus group and from 5.2 to 2.4 in the placebo group. Forty percent of patients in the pimecrolimus group and 11% of patients in the placebo group improved at least 50% in only 1 week. Follow-up lasted 8 weeks after treatment suspension. Perioral dermatitis relapsed in 10 patients treated with pimecrolimus and in six patients treated with placebo. Maximal benefit was seen in patients with a history of topical corticosteroid use [6].

### Drawbacks

A total of nine patients treated with pimecrolimus cream 1% and seven patients in the placebo group complained of adverse events, mainly erythema, burning sensation, and itching. Three patients treated with pimecrolimus and one with vehicle developed herpes simplex [6,7].

### Comment

These studies show that pimecrolimus cream 1% applied twice a day for 4 weeks works better than the vehicle. It leads to a more rapid improvement of perioral dermatitis, already seen after 1 week. Pimecrolimus cream seems to be more effective in patients with a history of use of topical corticosteroids.

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### Key points

- Six RCTs have been conducted to determine appropriate therapies for the treatment of perioral dermatitis.
- It appears that tetracycline has been used as a standard treatment in adults with some efficacy, as reported in three RCTs.
- Topical 1% metronidazole cream has been shown to be effective in one RCT.
- Recently, topical 1% pimecrolimus cream has been shown to be effective in two RCTs.
- Most of the available evidence for these and other treatments comes from case series.



# Hand eczema

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## Introduction

### Definition

The term “hand eczema” implies an inflammation of the skin (dermatitis) that is generally confined to the hands, but sometimes the feet are involved as well. Clinically, the condition is characterized by signs of redness, vesicles (tiny blisters), papules, edema, scaling, fissures (cracks), erosions, and hyperkeratosis (callus-like thickening), all of which may be present at different points in time (Figure 22.1). Itch, sometimes severe, is a common feature. Fissures and blisters might be painful and impair manual work.



**Figure 22.1** Hand eczema: redness, erosions, and tiny blisters, accompanied by severe itching.

Microscopically, the disease is characterized by spongiosis with varying degrees of acanthosis, and a superficial perivascular infiltrate of lymphocytes and histiocytes.

### Incidence and prevalence

Hand eczema is considered a common condition, with a point prevalence of 1–5% among adults in the general population, and a 1-year prevalence of up to 10%, depending on whether the disease definition includes more pronounced or mild cases [1]. The prevalence may be higher in some countries. Hand eczema is twice as common in women as in men, with the highest prevalence in young women. The reasons for this sex difference are unknown, although

greater exposure of women to wet work is probably contributory. Reliable data on the incidence are scarce, and are mainly confined to estimates in particular occupational groups. The incidence of notified work-related cases is between 0.7 and 1.5 cases per 1000 workers per year with much higher annual incidences among high-risk occupations, such as bakers and hairdressers [2].

### Etiology

The etiology is multifactorial. Contact irritants are the commonest external causes. Hand eczema caused by such irritants, or mild toxic agents, is known as irritant contact dermatitis. Water is a contact irritant, and thus an external causal or contributing factor. Causal factors that are less common than irritants are contact allergens. Hand eczema caused by skin contact with allergens is called allergic contact dermatitis. Ingested allergens (for example, nickel) may also provoke hand eczema. Being atopic (to produce immunoglobulin E (IgE) antibodies in response to ordinary exposures to allergens, usually proteins and, as a consequence, the tendency to develop asthma, rhinoconjunctivitis, or eczema) is a major predisposing factor responsible for hand eczema. A combination of the above-mentioned factors appears to play a role in many patients.

Hand eczema can be classified by etiology: irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis, or a combination of these types. A morphological classification of hand eczema is: vesicular hand eczema (dyshidrotic, pompholyx), hyperkeratotic hand eczema, fingertip dermatitis (pulpitis), nummular hand eczema, interdigital eczema, and dry fissured hand eczema.

### Prognosis

When there is a single, easily avoidable contact allergic factor, the prognosis is good. Several studies, however, have suggested that hand eczema tends to run a long-lasting and chronic relapsing course, probably because of the multifactorial origin.

### Diagnostic tests

The diagnosis is mainly based on history and clinical signs; there are no standardized diagnostic criteria. Patients are patch-tested to detect or rule out a contact allergy. In addition, prick tests or determination of specific IgE are performed to detect atopy, and skin scrapings are performed to rule out a mycotic infection. In the majority of cases, no relevant contact allergy can be detected. Specific prick tests of specific IgE are of additional value only in

very special cases (contact urticarial reactions that can become eczematous; protein contact dermatitis).

Differential diagnostic psoriasis, mycosis, lichen planus, scabies, granuloma annulare, herpes simplex, and artefacts might be considered.

## Treatment

The treatment of hand eczema is aimed at reducing clinical symptoms (including the disabling itch), preventing relapses, and reducing the burden of disease by allowing the resumption of everyday manual tasks. The outcome of the treatment can be assessed in different ways. Relevant outcome parameters include:

- the percentage of patients reporting a good/excellent response;
- the percentage of patients with an investigator-reported good/excellent response;
- reduction in severity (patient-rated and physician-rated scoring systems);
- dose reduction;
- time until relapse.

## Objectives

In daily practice, we often ask ourselves what treatment would be best for the patient with hand eczema who is sitting in front of us. This usually involves a comparison between different treatment modalities. Against this background, we formulated 14 clinically relevant questions.

Because of the tendency of hand eczema to develop a chronic or relapsing course, all of the questions are concerned with chronic hand eczema. In the context of this chapter, chronicity can arbitrarily be defined as a duration of more than 6 months.

## Methods of search

Controlled trials dating back to 1977 were located by searching the Skin Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Embase in February 2013 for original articles in English, French, German, or Dutch. Uncontrolled trials were discarded, unless systematic reviews and controlled trials were lacking on a specific subject. Also, papers studying different dermatoses and not specifically stating the results for the patients with hand eczema were ignored. The questions were formulated before the search, and only papers pertaining to these questions were included.

## Questions

Because of the tendency of hand eczema to develop a chronic or relapsing course, all of the questions considered below deal with chronic hand eczema, arbitrarily defined as a duration of more than 6 months. Prescription of topical corticosteroids is at present the most common treatment; therefore, it is the major comparator in the questions listed below.

- In adults with chronic hand eczema, do topical coal-tar preparations lead to a better patient-rated or physician-rated reduction in symptom scores than topical corticosteroids?
- In adults with hyperkeratotic hand eczema, does dithranol lead to an improvement in patient-rated and physician-rated symptom scores and longer remission periods after clearance in comparison with topical corticosteroids?
- In adults with chronic hand eczema, do short bursts of potent topical corticosteroids (class 3 or 4) lead to better patient-rated or physician-rated symptom scores than continuous mild (class 1 or 2) topical steroids?

- In adults with chronic hand eczema, are oral immunosuppressive agents (ciclosporin, methotrexate, mycophenolate mofetil, azathioprine) better in maintaining a long-term (more than 6 months) reduction of patient-rated or physician-rated symptom scores than topical corticosteroids?
- Is the treatment of chronic hand eczema with local psoralen-ultraviolet A (PUVA) or ultraviolet B (UVB) irradiation better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?
- In adults with chronic hand eczema, does treatment with PUVA irradiation (oral or topical psoralen) lead to a better reduction in patient-rated and physician-rated symptom scores and remission periods than UVB irradiation?
- In adults with chronic hand eczema, is oral treatment with retinoids better in terms of patient-rated and physician-rated symptom scores than topical corticosteroids?
- Is the treatment of chronic hand eczema with calcineurin inhibitors better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?
- In adults with dyshidrotic hand eczema, does iontophoresis lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical steroids or UVB/PUVA irradiation?
- In adults with relapsing vesicular hand eczema based on contact allergy to nickel, does dietary intervention or oral therapy with chelating agents lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical corticosteroids?
- Does the daily application of a bland emollient lead to dose reduction and/or frequency reduction of topical corticosteroids in adults with chronic hand eczema?
- In adults with chronic clinically active hand eczema, do protective or occlusive gloves or barrier creams lead to better patient-rated or physician-rated symptom scores than topical steroids?
- Does the addition of a topical antibacterial agent to topical corticosteroids result in better patient-rated or physician-rated symptom scores than topical corticosteroids alone?
- In patients with chronic hand eczema, is an educational intervention program effective for secondary and tertiary prevention on hand eczema compared with limited education as usual?

## In adults with chronic hand eczema, do topical coal-tar preparations lead to a better patient-rated or physician-rated reduction in symptom scores than topical corticosteroids?

One clinical trial was identified on the effect of coal tar. Additional trials may be found in the older literature (pre-1977).

### Efficacy

No systematic reviews were found.

### Coal tar

In a self-controlled, randomized study, the efficacy of coal tar paste with zinc oxide paste was compared with betamethasone valerate 0.1% in 19 patients with a within-patient design. Coal tar gave significant improvement compared with baseline, but no significant difference was observed between the treatments [3].

### Drawbacks

Six participants dropped out because they experienced problems with wearing hand gloves (problems were not specified). One

participant dropped out due to pompholyx as a result of contact allergy to 5% coal tar.

### Comment

Small number of participants ( $n = 19$ ) with relatively high drop-out rate ( $n = 7$ ). The results are listed as overall mean scores and no exact data are given.

### Implications for clinical practice

The scientific-based evidence for coal tar treatment is scarce; however, trials may be found in the earlier literature (pre-1977). Contrary to belief, coal tar is not associated with an increased risk of cancer [4].

### In adults with hyperkeratotic hand eczema, does dithranol lead to an improvement in patient-rated and physician-rated symptom scores and longer remission periods after clearance in comparison with topical corticosteroids?

No systematic reviews were found, and no trials (controlled or uncontrolled) of dithranol for any type of hand eczema were identified. Trials may be found in the earlier literature (pre-1977).

### In adults with chronic hand eczema, do short bursts of potent topical corticosteroids (class 3 or 4) lead to better patient-rated or physician-rated symptom scores than continuous mild to moderate (class 1 or 2) topical steroids?

We found no studies comparing the effect of short bursts of strong (class 3 or 4) topical corticosteroids (for example, twice weekly, or at weekends only) with continuous application of milder (class 1 or 2) topical corticosteroids. One randomized controlled trial (RCT) compared thrice-weekly application versus weekend application of the same steroid, with limited evidence that the thrice-weekly application was better.

### Efficacy

No systematic reviews were found.

### Thrice-weekly versus weekend application

There is limited evidence of a preferential effect of thrice-weekly application of mometasone in a parallel group RCT with 106 participants in a 30-week maintenance phase (i.e., after induction of remission) [5].

### Once-daily versus twice-daily application

In a controlled trial with once-daily halcinonide 0.1% versus twice-daily betamethasone dipropionate 0.05% both showed good efficacy in 53 participants during 4 weeks [6]. In half of the patients, once-daily halcinonide 0.1% was superior.

### Two different concentrations

One left–right RCT of 2 weeks' duration comparing different concentrations of the same corticosteroid applied twice daily detected no difference in 46 participants [2].

### Class 2 versus class 3 corticosteroids

One RCT compared short-term (3 weeks) application of fluprednide acetate 0.1% cream (class 2) with betamethasone valerate 0.1% cream (class 3), both in a once-daily regimen in 76 participants [7]. There were no differences in the time to onset of effect or clinical efficacy.

### Class 2 versus class 4 corticosteroids

In a double-blind left–right RCT with 61 participants, more patients remained free of relapses with clobetasol propionate than with fluprednide acetate [8]. In addition, the time to relapse was longer with clobetasol propionate. Treatment initially and in case of recurrence was twice daily; in the maintenance phase, the application was twice weekly. The side effects were comparable between the two groups.

### Drawbacks

Mild skin atrophy was reported in two studies [5,8].

### Comment

With the exception of the study on thrice-weekly versus weekend application, all of the studies were of short duration. The primary outcome was not always clearly stated, and some studies included patients in relapse. None of the studies investigated tachyphylaxis or atrophy. Earlier reports (pre-1977) may provide some insight into this issue.

### Implications for clinical practice

The appropriate choice of an optimal topical steroid treatment schedule cannot be derived from the current literature on hand eczema trials. Evidence from studies on other eczematous diseases may have to be considered.

### In adults with chronic hand eczema, are oral immunosuppressive agents (cyclosporin, methotrexate, mycophenolate mofetil, azathioprine) better in maintaining a long-term (more than 6 months) reduction of patient-rated or physician-rated symptom scores than topical corticosteroids?

One RCT was identified, showing that cyclosporin was effective, but not significantly better in terms of clinical signs or quality of life. One RCT concluded that azathioprine is an effective adjunctive treatment option. We identified no RCTs studying other oral immunosuppressive agents.

### Efficacy

No systematic review was found.

### Cyclosporin versus topical betamethasone

An RCT compared cyclosporin with betamethasone dipropionate 0.05% twice daily in 41 participants [9]. The study had three phases, none of which showed a comparative advantage in terms of clinical signs, global assessment, or cumulative relapse rate. The first treatment phase was 6 weeks; the second and third amounted to 30 weeks.

### Methotrexate

We identified no controlled trials.

An uncontrolled case study showed low-dose methotrexate to be effective in five patients with recalcitrant palmoplantar pompholyx [10].

### Mycophenolate mofetil and azathioprine

We identified no controlled trials.

### Azathioprine as adjunctive

One RCT compared the additional value of azathioprine to topical clobetasol propionate 0.05% cream with topical clobetasol

propionate monotherapy in 108 patients with chronic hand eczema for 24 weeks [11]. This study reported a significant better improvement with regard to hand eczema severity index score and itch in the azathioprine group.

### Drawbacks

Paresthesia (“tingling”), dizziness, facial edema, and increase in serum creatinine were reported during ciclosporin use. Surprisingly, no side effects were reported for azathioprine.

### Comment

The comparator in the ciclosporin studies was a relatively strong corticosteroid.

### Implications for clinical practice

Ciclosporin may be useful for achieving short-term control, but cannot be recommended for maintenance therapy. Long-term side effects such as blood dyscrasia, renal failure, increased blood pressure, and skin malignancies are of major concerns. Choices regarding systemic treatment of hand eczema cannot be derived from the current literature on hand eczema trials.

### Is the treatment of chronic hand eczema with local psoralen+ultraviolet A or ultraviolet B irradiation better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?

We identified no trials explicitly comparing PUVA or UVB therapy with topical corticosteroids; only one RCT had ordinary topical treatment with emollients as the comparator. Several controlled trials were identified that compared the efficacy of PUVA, UVB, or UVA1 therapy with a control group or using a left–right design. There is insufficient evidence that PUVA or UVB therapy is more effective than conventional topical corticosteroid therapy.

### Efficacy

No systematic reviews were found.

### Topical psoralen+ultraviolet A

In a double-blind randomized within-patient trial of 15 patients with chronically relapsing vesicular hand eczema, topical PUVA and UVA treatment showed improvement of the severity score over the 8-week treatment period, but no statistical difference between the treated hands at any stage [12].

In a controlled clinical trial (CCT) with a left–right design, topical cream PUVA was compared with UVA1 [13]. The study comprised 27 patients with bilateral dyshidrotic hand eczema. Almost all patients showed a good response to both treatments, with a reduction of physician-rated scores of 50%. There were no statistically significant differences between the left and right hands.

In an observer-blinded, left–right design, there was little difference between topical 8-methoxypsoralen (8-MOP) bath PUVA and topical 8-MOP lotion PUVA therapy in 24 patients with chronic hand or foot eczema; there was greater than 80% clearing with both modalities [14]. After 1 month, the most successful treatment was continued on both sides until the lesions cleared; there were no differences in the length of the relapse-free period.

An open-label RCT with 158 participants showed that oral PUVA at home was equally effective as topical bath PUVA in the hospital [15]. In addition, it appeared to result in lower costs and less time off work.

In a within-participant RCT with 15 participants, the effectiveness of middle-dose UVA1 irradiation was compared with topical cream PUVA therapy [16]. Treatment was given thrice weekly during a period of 5 weeks. Both groups improved, but there was no significant difference between the groups.

An observer-blinded RCT in 29 participants showed no significant difference between topical and oral psoralen, although oral PUVA might be preferred in hyperkeratotic hand eczema [17].

### Ultraviolet A1

In a double-blind RCT with 28 patients with dyshidrotic hand eczema, five-times weekly irradiation with UVA1 was compared with placebo [18]. After 1 week of treatment, a significant difference was seen between the two groups, with greater efficacy for UVA1.

### Ultraviolet B

Eighteen patients with chronic hand eczema resistant to potent topical corticosteroids were randomly divided into three treatment groups: UVB of the hands only, placebo irradiation, and whole-body UVB irradiation [19]. Local UVB irradiation of the hands was significantly better than placebo; whole-body UVB irradiation with additional irradiation of the hands was significantly better than continuing the local treatment alone (not specified), according to a simple clinical grading (cleared, improved, unchanged/worse). A 3-month follow-up period demonstrated fast relapse of the hand eczema.

In an RCT with 48 patients with occupational hand eczema, UVB at home 5 days a week for 8 weeks was compared with nonspecific topical treatment [20]. Physician-rated scores and transepidermal water loss improved in both groups, although the improvement did not reach statistical significance for most parameters.

### Drawbacks

Ultraviolet therapy can cause side effects such as burning episodes, subacute eczema, patchy hypopigmentation, and acute exacerbation of eczema. It may also induce skin cancer as a long-term effect.

### Comment

In some studies, patients continued their topical medication or emollients. There are no studies comparing PUVA, UVA1, or UVB therapy with the conventional topical corticosteroid therapy. There is also no evidence that ultraviolet therapy is the most effective for hand eczema (see the next question).

### Implications for clinical practice

PUVA and UVB are effective; UVA1 also appears to be effective. The choice of these treatment options is guided by considerations other than proven clinical superiority over other modalities.

### In adults with chronic hand eczema, does treatment with psoralen+ultraviolet A irradiation (oral or topical psoralen) lead to a better reduction in patient-rated and physician-rated symptom scores and remission periods than ultraviolet B irradiation?

We identified two RCTs on oral PUVA and two CCTs on oral/topical PUVA. The controlled trial on topical bath PUVA



demonstrated no comparative advantage, whereas the RCT on oral PUVA showed an effect in favor of PUVA.

### Efficacy

No systematic review was found.

### Topical bath psoralen+ultraviolet A versus ultraviolet B

A 6-week left–right design CCT including 13 patients showed that, although effective, topical bath PUVA was not better than UVB [21].

### Oral psoralen+ultraviolet A versus ultraviolet B

An RCT showed an effect in favor of oral PUVA in a 3-month study of 35 patients. In this study, only one hand was treated, but in most patients the untreated hand also improved [22].

In a 9-week RCT with left–right design, 15 patients were treated with local narrowband UVB or PUVA thrice a week. Both groups showed significant improvement compared with baseline and a local narrowband UVB phototherapy regimen is as effective as PUVA therapy in patients with chronic hand eczema of dry and dyshidrotic types [23].

A CCT comparing UVB used at home with PUVA at the clinic in 26 patients during approximately 10 weeks, showed no comparative advantage [24].

### Drawbacks

Nausea caused by the oral psoralen was reported. Pain, burning, itching, and redness were reported with both therapies, but slightly more from PUVA irradiation.

In both PUVA and UVB, mild xerosis was reported, which responded to emollients.

### Comment

Long-term adverse effects could not be assessed. Improvement of the untreated hand may be the result of compliance with topical emollients. More than 17 uncontrolled studies were identified, claiming a beneficial effect of ultraviolet treatment (PUVA or UVB), but there was no comparator in any of the studies.

### Implications for clinical practice

PUVA or UVB is effective in treating hand eczema. The question of which modality is better remains unsolved.

### In adults with chronic hand eczema, is oral treatment with retinoids better in terms of patient-rated and physician-rated symptom scores than topical corticosteroids?

We identified several trials on the use of retinoids in hand eczema; there were no trials comparing oral retinoids with corticosteroids. Both topical and oral treatment with retinoids appeared to be effective.

### Efficacy

No systematic reviews were found.

### Topical retinoid versus topical corticosteroids

In a symmetrical double-blind nonrandomized study, the efficacy of triamcinolone acetonide 0.1% cream was compared with the

same cream containing, in addition, 0.25% retinoic acid [25]. The study included 18 patients with different types of eczema (12 with atopic dermatitis, four with allergic contact dermatitis, one with nummular eczema, and one with dyshidrosis); the palms and soles were involved in only five patients. The duration of treatment was planned for 2 weeks, with the option of extending the treatment to 3 weeks. No statistically significant differences were observed between the treatments.

An open-label RCT with 55 patients compared bexarotene gel monotherapy (ligand for retinoid X receptors) with the same gel in combination with either mometasone furoate 0.1% ointment or with hydrocortisone acetate 1% ointment [26]. The steroids were applied twice daily, whereas bexarotene gel was applied in an increasing regimen, starting at once every other day up to three times daily, unless adjustment was needed because of irritation. All groups showed a meaningful decrease in physician-rated scores, without significant differences between the groups.

### Oral retinoids

An RCT including 29 patients with hyperkeratotic hand eczema compared once-daily 30 mg acitretin with placebo [27]. A significant improvement in comparison with the placebo group was seen in relation to hyperkeratosis, fissures, and scaling, but not in relation to itch, redness, or vesicles. The improvement occurred in the first 4 weeks, with no additional effect seen in the following 4 weeks.

A multicenter, double-blind RCT assessed the efficacy of three different dosages of 9-*cis*-retinoic acid (alitretinoin) and placebo [28]. The 319 patients were equally randomized over four groups: oral alitretinoin 10 mg/day, 20 mg/day, 40 mg/day, and placebo. Alitretinoin led to a significant and dose-dependent improvement in the physician-rated score.

In a large randomized trial alitretinoin (10 or 30 mg per day for up to 24 weeks) was superior to placebo in 1032 patients with chronic severe hand eczema [29]. Of the patients treated with 30 mg alitretinoin, 40% rated their hand eczema as “clear” or “almost clear” at the end of therapy. In the 10 mg group this was 24% and in the placebo group 15%. In an extended open-label trial, 243 patients received 30 mg alitretinoin and the drugs remained well tolerated for overall treatment durations of up to 48 weeks [30]. In addition, the beneficial effects of alitretinoin over placebo were confirmed in a retreatment trial among a subgroup of 117 patients who had relapsed [31].

### Drawbacks

Topical use of retinoic acid plus corticosteroids is reported to cause significantly more subjective irritation than topical corticosteroids without retinoic acid [25,26].

Side effects of oral acitretin are common and almost all patients experience dry skin (especially the lips). The side effects were dose dependent; the most frequently reported were headache (14%, but this was also reported in the placebo group), mucocutaneous signs as dry lips (5%), and flushing (3%). Clinically insignificant increases in serum triglyceride, cholesterol, and creatinine kinase were reported in several trials on alitretinoin. Central hypothyroidism, with no clinical expression, was observed more rarely. Several papers studied the safety of oral alitretinoin, reporting comparable side effects [32,33].

### Comment

Oral 9-*cis*-retinoic acid appears to be a promising treatment option, but it remains to be demonstrated that this drug is more effective



than conventional topical corticosteroids or UVB/PUVA therapy. In addition, evidence of the efficacy and safety of alitretinoin beyond 48 weeks and of the efficacy in vesicular hand eczema is lacking. A pregnancy prevention program is mandatory for women of fertile age because of the teratogenicity of oral retinoids.

### Implications for clinical practice

Oral retinoids appear to be effective in hand eczema, especially in hyperkeratotic hand eczema. However, as there is no comparison with conventional therapy, it is unclear whether it should be a therapy of first choice.

### Is the treatment of chronic hand eczema with calcineurin inhibitors better in reducing patient-rated and physician-rated symptom scores than topical corticosteroids?

Two RCTs were found that compared the efficacy of topical tacrolimus with mometasone furoate, which appeared to be equivalent and in two RCTs tacrolimus was significantly more effective than vehicle. Two RCTs compared topical pimecrolimus with vehicle cream.

### Efficacy

No systematic reviews were found.

### Tacrolimus

Sixteen patients were included in a left–right RCT comparing topical tacrolimus 0.1% ointment with mometasone furoate 0.1% ointment (a class III corticosteroid) [34]. The treatment period was 4 weeks, with a follow-up period up to 8 weeks. Both treatments led to a statistically significant decrease in clinical severity, with no significant differences between the groups.

In another RCT, topical tacrolimus 0.1% was compared with mometasone furoate in 30 patients for 90 days [35]. Both treatments showed similar therapeutic results.

A randomized pilot study in 32 patients with moderate to severe hand eczema suggested that tacrolimus might prolong the time until relapse compared with vehicle cream during 14 weeks [36].

In an RCT, 28 participants with moderate to severe nickel sulfate-induced allergic hand eczema were treated with 0.1% tacrolimus ointment twice daily versus twice daily vehicle ointment during 14 days. The symptom scores were significantly lower in the tacrolimus group compared with the vehicle group during treatment and 7 days afterwards [37].

### Pimecrolimus

In a multicenter RCT, 294 patients with hand eczema were allocated to up to 3 weeks' treatment with pimecrolimus 1% cream or to vehicle [38]. Twice-daily application of the study creams (evening application under occlusion) was continued until clearance or completion of 3 weeks' treatment. The efficacy of pimecrolimus 1% cream increased over time, while that of the vehicle stagnated after the second week. There were no statistically significant differences between the two groups, unless stratification for palmar involvement was applied; pimecrolimus 1% cream was superior in these patients.

In a multicenter, double-blind, RCT 652 patients were treated for 6 weeks with pimecrolimus 1% or vehicle cream twice daily with overnight occlusion, followed by a 6-week open-label pimecrolimus treatment [39]. There were no significant differences with regard to disease signs; however, pruritus relief was significantly better in the pimecrolimus group.

### Drawbacks

Tacrolimus 0.1% ointment produced stinging upon application; with pimecrolimus 1% cream, however, this was uncommon (0.7% vs 2.1% in the vehicle group) or comparable to the vehicle cream [39].

### Comment

The effect of pimecrolimus 1% cream in comparison with the vehicle might have reached significance if the follow-up period had been longer, as the efficacy of pimecrolimus 1% cream increased over time. Pruritus relief was greater in the pimecrolimus group, but the other studies did not include patient-rated scores.

### Implications for clinical practice

Topical tacrolimus is more effective than vehicles, but is at best equally effective as topical corticosteroids. Pimecrolimus is as effective as vehicles. With the present evidence, calcineurin inhibitors may be used for rotational therapy with topical corticosteroids, with potent corticosteroids for (severe) exacerbations and topical calcineurin inhibitors in the maintenance phase and for mild exacerbations.

### In adults with dyshidrotic hand eczema, does iontophoresis lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical steroids or ultraviolet B/psoralen+ultraviolet A irradiation?

We identified only one RCT using iontophoresis in patients with dyshidrotic hand eczema, showing a significant improvement on the iontophoresis-treated side in comparison with the untreated side. We found no trials comparing iontophoresis with topical corticosteroids or UVB/PUVA therapy.

### Efficacy

No systematic reviews were found.

### Iontophoresis versus no treatment

In a randomized left–right comparison, the effects of tap-water iontophoresis in addition to steroid-free topical therapy were investigated in 20 patients with dyshidrotic hand eczema [40]. After 3 weeks (20 iontophoresis applications), the parameters “itching” and “vesicle formations” scored significantly better on the iontophoresis-treated side than on the untreated side, but redness and desquamation did not differ significantly.

### Drawbacks

Tap-water iontophoresis was always associated with subjective sensations such as stinging and discrete paresthesia (“tingling”). No severe side effects or possible harmful effects were reported.

### Comment

We found insufficient evidence for the benefit of additional iontophoresis therapy in comparison with conventional corticosteroid or UVB/PUVA therapy.

### Implications for clinical practice

Iontophoresis appears to be harmless, but has not been proved to be effective.

### **In adults with relapsing vesicular hand eczema based on contact allergy to nickel, does dietary intervention or oral therapy with chelating agents lead to an improvement in patient-rated and physician-rated symptom scores in comparison with topical corticosteroids?**

We identified three small RCTs and one CCT. None of the studies compared the intervention with topical corticosteroids. An RCT on triethylenetetramine found no significant improvement of hand eczema. Another RCT, on tetraethylthiuram disulfide (disulfiram), found only very limited evidence in favor of this treatment. One controlled trial found no evidence that a low-nickel diet improves dyshidrotic hand eczema.

#### **Efficacy**

No systematic reviews were found.

#### **Oral therapy with a nickel-chelating compound**

In a multicenter, randomized, double-blind, crossover study, oral treatment with triethylenetetramine 300 mg daily for a 6-week period or placebo were given to 23 nickel-positive patients with chronic hand eczema [41]. No significant improvement occurred in hand eczema on the basis of either the patients' or the doctors' evaluations. The study was terminated prematurely because of literature reports on teratogenicity in rats.

In a double-blind, placebo-controlled RCT, tetraethylthiuram disulfide at a gradually increased dosage was given for at least 6 weeks after the full dosage of 200 mg had been reached [42]. During the treatment period, the hand eczema healed in five of the 11 patients treated with tetraethylthiuram disulfide in comparison with two of 13 in the placebo group (not significant). Using a semi-quantitative scoring system, the results in favor of tetraethylthiuram disulfide were statistically significant for scaling and frequency of flares, but not for the sum of the parameters.

#### **Low-nickel diet**

In a probably nonrandomized trial including 24 patients with dyshidrotic hand eczema caused by nickel, the effects of a low-nickel diet for 3 months (eight patients) were compared with oral disodium cromoglycate for 3 months (nine patients) and with seven patients who did not give consent to the study and did not receive any treatment [43]. All 24 patients were evaluated blindly for itching and number of vesicles. The low-nickel diet did not lead to improvement in these patients, but those treated with disodium cromoglycate improved significantly and had fewer vesicles than the controls and the patients treated by diet.

#### **Combination**

A randomized placebo-controlled trial including 21 patients with chronic vesicular hand eczema with nickel sensitivity stated that the combination of low-nickel diet and short course of oral disulfiram therapy reduced severity of hand eczema statistically after 4 weeks [44].

#### **Drawbacks**

One patient treated with disulfiram had toxic hepatitis after 8 weeks of treatment and two of 30 patients showed signs of hepatic toxicity [42]. Another RCT only noted slight, transient elevation of liver enzymes after 4 weeks [44]. The study on triethylenetetramine was ended prematurely due to a literature report on teratogenicity in

rats [41]. No studies using a low-nickel diet assessed possible harmful effects.

#### **Comment**

None of the trials showed sufficient evidence for the benefit of either a low-nickel diet or a nickel-chelating compound. Only four CTs with small numbers of patients were carried out. On the basis of the harm and possible side effects, oral treatment with a nickel-chelating compound cannot be recommended. None of the trials compared treatments with conventional topical medication (for example, corticosteroids).

#### **Implications for clinical practice**

Given the side effects and the lack of efficacy, oral therapy with a nickel-chelating compound cannot be recommended. There is no evidence that a low-nickel diet improves pompholyx-type hand eczema.

### **Does the daily application of a bland emollient lead to dose reduction and/or frequency reduction of topical corticosteroids in adults with chronic hand eczema?**

One RCT and two uncontrolled studies compared emollients with topical corticosteroids, showing better clinical assessments for emollients, albeit not significant.

#### **Efficacy**

No systematic review was found.

#### **Emollient versus topical corticosteroids**

A double-blind RCT of 2 weeks' duration compared twice-daily application of betamethasone valerate 0.1% with once daily application of betamethasone valerate 0.1% in addition to maintenance therapy with a 5% urea-containing moisturizer in 44 participants. Once-daily treatment combined with emollients showed a better clinical assessment (albeit not statistically significant) compared with twice-daily treatment, especially in the group of patients with a moderate eczema at inclusion [45].

#### **Versus each other**

In one left-right RCT with 30 participants, using patient preference as the outcome parameter, there was limited evidence in favor of Aquacare-HP over Calmurid, both of which contain 10% urea [46].

An RCT in 32 participants confirmed that the frequent application of emollients resulted in better hand eczema scores [47]. However, a superior effect of emollient with ceramides versus a regular petrolatum-based emollient was not demonstrated. This RCT showed that an emollient with ceramides was able to reduce the use of topical corticosteroids.

The beneficial effect of emollients on hand eczema was also seen in a CCT comparing two bland emollients [48]. There was a decrease in transepidermal water loss, as well as an improvement in physician-rated and patient-rated severity scores.

Uncontrolled studies noted a reduction in steroid use in patients treated with a moisturizing cream and in patients treated with a protective foam in 31 and 37 patients [49,50].

#### **Drawbacks**

No major side effects were reported. Burning and worsening of the preexisting hand eczema were reported [46]. Patients were concerned about greasiness of their hands and with staining of objects they handled.

## Comments

Several poor-quality uncontrolled studies were also identified, none of which had steroid dose reduction as the outcome parameter.

## Implications for clinical practice

Despite the widespread use of emollients, there is only little evidence of any steroid-sparing or additive effect in the treatment of hand eczema. In general, there seems to be no harm either, apart from occasional contact allergy against an ingredient.

## In adults with chronic clinically active hand eczema, do protective or occlusive gloves or barrier creams lead to better patient-rated or physician-rated symptom scores than topical steroids?

Information on avoidance of allergens or irritants on a case-by-case basis can be found in the major textbooks on contact dermatitis. The effect of emollients was covered in the previous question. One controlled trial on protective creams was found. We found a few uncontrolled, rather descriptive studies indicating some benefit of gloves and/or barrier creams, and one study used a within-patient left-right design [51,52].

## Efficacy

A number of issues in connection with this question are dealt with in a Cochrane systematic review on irritant hand eczema [53]. They concluded that industrial barrier creams may have a similar role as emollients in the prevention of occupational contact dermatitis; however, there is insufficient evidence that it has a long-term protective effect.

## Barrier creams

In a randomized open trial in 53 patients a barrier-strengthening moisturizer (5% urea) seemed to prolong the disease-free interval in patients with controlled hand eczema compared with no treatment at all (20 vs 2 days) [54].

## Comments

Protective gloves offer protection when manual (wet) tasks are performed; however, prolonged occlusion may be a risk factor for hand eczema [55]. Based on practical experience, supported by an experimental study on the healthy skin of volunteers, a cotton lining or inner glove is recommended [56].

## Implications for clinical practice

Insufficient evidence for long-term protective effect.

## Does the addition of a topical antibacterial agent to topical corticosteroids result in better patient-rated or physician-rated symptom scores than topical corticosteroids alone?

No trials compared the additional effect of topical antibacterial agents with topical corticosteroids alone. Only one RCT comparing betamethasone cream with the addition of either fusidic acid or clioquinol was found, showing a similar effect on clinical severity.

## Efficacy

No systematic reviews were found.

## Addition of fusidic acid or clioquinol to betamethasone

In a multicenter open-label RCT with 120 patients, 4 weeks' twice-daily application of betamethasone 0.1% clioquinol 3% cream was

compared with betamethasone 0.1% fusidic acid 2% cream [57]. The two preparations were equally effective in reducing the observer-rated severity score. However, the combination of betamethasone cream and fusidic acid produced a better bacteriological response.

## Drawbacks

Betamethasone 0.1% fusidic acid 2% cream was considered more cosmetically acceptable than the preparation with clioquinol. The difference was statistically highly significant. Staining of the skin and clothing were the major problems.

## Comment

Staphylococcal superantigens in infected areas elsewhere on the body, although the study protocol allowed them to be treated, might have had an effect on the hands.

## Implications for clinical practice

There were no comparisons of a corticosteroid with a combination of corticosteroid and antibacterial agents. Evidence of an additional effect of antibacterial agents in patients with hand eczema is still lacking.

## In patients with chronic hand eczema, is an educational intervention program effective for secondary and tertiary prevention on hand eczema compared with limited education as usual?

Several RCTs have been conducted on primary prevention, and a systematic review concluded that there is moderate evidence for the effectiveness of primary prevention programs. However, there is low evidence for the effect on improving clinical and self-reported outcomes [58]. We identified two RCTs, one CCT, and one controlled trial on secondary or tertiary prevention.

## Efficacy

A Cochrane review concluded that, although the findings of the review were generally positive, there is insufficient evidence, at present, for the effectiveness of most of the treatments identified for primary prevention of occupation-induced hand eczema in the workplace [53]. No systematic reviews were identified on secondary or tertiary prevention.

## Education programs

An RCT in 255 hospital workers with symptoms of hand eczema showed a beneficial effect of skin care education and individual counseling compared with care as usual (only topical steroids, emollients, and care by general practitioner) after 6 months [59].

In a CCT, 209 geriatric nurses with hand eczema received either care as usual by a dermatologist or a personalized secondary intervention program with education concerning barrier cream and gloves with lectures and hands-on training during four visits. After 3 months the hand eczema significantly improved in the intervention group. More nurses were able to continue their job because of the intervention program compared with those without the program (96 vs 86%) [60].

The Tertiary Individual Prevention study is a multicenter trial with an interdisciplinary, integrated inpatient rehabilitation measure with 3 weeks of inpatient treatment. The 1-year data from 1617 individuals revealed a significant reduction in the severity of occupational skin diseases, the use of topical corticosteroids, and days

of sick leave: 87.4% were able to return to work and to remain in the workforce [61].

### Integrated care

A multicenter RCT with 196 patients received usual care by a dermatologist or integrated care. The integrated care included allergo-dermatological evaluation by a dermatologist, occupational intervention by a clinical occupational physician, and counseling by a specialized nurse on optimizing topical treatment and skin care. After 26 weeks the intervention group scored significantly better on clinical effectiveness, but not on quality of life and days of sick leave [62].

### Drawbacks

Participation in the TIP study was voluntary, but patients were obliged to cooperate with the respective insurance organizations, which makes it difficult to compare this study with other countries.

### Comment

In several studies, no comparator was used. It is difficult to compare different educational programs and to implement in daily practice. Three weeks of inpatient treatment might not be feasible in every setting.

### Implications for clinical practice

Education and counseling seems to improve the effectiveness of hand eczema care and prevent relapse; however, long-term efficacy is still under investigation.

#### Key points

- There is insufficient evidence on which to base a choice between short bursts of potent topical corticosteroids compared with continuous application of mild corticosteroids.
- There is insufficient evidence for oral immunosuppressants as maintenance therapy.
- There is little evidence of a steroid-sparing effect of emollients, although these are widely prescribed.
- PUVA and UVB are effective, but there is no evidence of a clinical advantage of one modality over the other.
- Oral retinoids appear to be effective and well tolerated in hand eczema, especially in hyperkeratotic hand eczema.
- There is insufficient evidence of an additive effect of iontophoresis.
- There is insufficient evidence for a low-nickel diet or chelating agents in hand eczema accompanied by nickel allergy.
- There is insufficient evidence of an additive effect of topical antibacterial agents.
- There is insufficient evidence of the superiority of topical calcineurin inhibitors to topical corticosteroids.
- Education for secondary and tertiary prevention seems to be effective; however, long-term data are needed.

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# The primary prevention of atopic dermatitis

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## Background

### The global health burden of atopic dermatitis

The high disease prevalence, socioeconomic costs, and lack of curative therapy make the primary prevention of atopic dermatitis (atopic eczema) an important public health goal. Atopic dermatitis is a global problem increasing in prevalence in many parts of the world [1]. Prevalence rates approach 18–20% in areas of North America, Europe, and Asia. Children suffering from atopic dermatitis experience quality-of-life deficits equal to, or greater than, many chronic childhood diseases such as diabetes [2]. Children with atopic dermatitis have an increased susceptibility for developing other so-called “atopic diseases,” including food allergy, allergic rhinitis, and asthma [3]. In addition to the atopic diseases, other comorbidities associated with atopic dermatitis include a susceptibility to skin infections and sleep and psychological disturbances, especially in patients with severe disease. Whether measures that reduce the burden of atopic dermatitis also reduce the risk of these downstream consequences is not known.

### Target populations

Children at high risk for the development of atopic dermatitis remain best identified by the presence of a family history of atopic diseases, although a consensus definition of “high risk” is still lacking [4]. A parental history of atopic dermatitis specifically, as opposed to other atopic diseases, may be the strongest predictor, with the risk more than doubling in some studies [5,6]. Wen *et al.* developed a model to improve the accuracy of atopic dermatitis prediction that combines family history with environmental factors although the model needs further confirmation [7]. Filaggrin (FLG) genotype will likely play an important role in predictive models in the future. Brown *et al.* found FLG defects, especially homozygous mutations, to be highly penetrant for flexural eczema development in an unselected population-based cohort [8]. New predictive models that incorporate both FLG genotype and environmental factors utilizing birth cohorts are eagerly awaited. Several cord blood markers have also been evaluated (e.g., immu-

noglobulin E (IgE) levels, interferon-gamma, interleukin-4) but are poorly predictive of atopic dermatitis development or are not practical for routine use. Of note, while identifying high-risk populations is an important component of disease prevention, Mar and Marks estimate that a large proportion of new cases of atopic dermatitis arise from low-risk populations [9].

### Prevention approaches

Because elevated serum IgE levels commonly accompany atopic disorders, most prevention strategies have focused on preventing IgE sensitization. Indeed, multifaceted allergen avoidance strategies have been modestly successful in the primary prevention of asthma [10]. As detailed in this chapter, these allergen avoidance strategies have been less successful in the prevention of atopic dermatitis. One reason for this lack of success may be that IgE sensitization does not play a central role in the *initiation* of atopic dermatitis. In some areas of the world, flexural eczema is not associated with allergic sensitization at all [11]. Mouse models of FLG deficiency and some human studies suggest IgE sensitization may be the consequence of a skin barrier defect, with sensitization occurring through the skin [12,13]. The exact combination of factors that initiate atopic dermatitis are unknown and may vary by individual, making the design of novel prevention approaches challenging.

### Emerging research

Newer approaches to atopic dermatitis prevention are under study. The recent discovery that defects in the skin barrier gene FLG predispose to the development of atopic dermatitis has led to a renewed focus on the skin barrier in atopic dermatitis treatment and prevention [14]. Other approaches, such as attempting to alter the gut's microbiota, may help blunt pathologic inflammatory responses. Research is uncovering gene–gene and gene–environment interactions that likely contribute to disease pathogenesis [15,16]. A better understanding of how the skin barrier, the immune system, and the environment interact in this disease will hopefully lead to novel and more effective prevention strategies for all the atopic disorders.

## Methods of search

This review utilized the mapping exercise of systematic reviews for atopic dermatitis conducted by the Centre of Evidence Based Dermatology at the University of Nottingham [17]. This collection is derived from a systematic and comprehensive search of the literature that is designed to identify all systematic reviews on the epidemiology, treatment, and prevention of atopic dermatitis. Databases searched include the Cochrane Database of Systematic Reviews, Embase, and Medline/PubMed. The most recent search was performed in August 2012. Additional PubMed and Google Scholar searches were performed up to 31 October 2012 to identify individual randomized controlled trials (RCTs) published after the most recent systematic review. Our recommendations are based on the most recently published systematic review(s) that were deemed to be at least of moderate quality as assessed using the AMSTAR quality rating system [18] and any subsequently published RCTs.

## Questions

### Will exclusive breastfeeding for at least 4 months reduce a child's risk of developing atopic dermatitis?

Breast milk contains many factors that may protect against the development of inflammatory disease, such as immunoglobulins, cytokines, and omega fatty acids. Additionally, breastfeeding may establish a beneficial intestinal microbiota in the infant that protects against certain diseases [19].

#### Efficacy

Several systematic reviews and guidelines of care were identified in the literature [20–29]. Most of these reports either state that there is a protective effect of exclusive breastfeeding in the first 3–4 months of life or there is a lack of evidence. The most recent systematic review by Yang *et al.* reviewed 21 prospective cohort studies. If studies by Chandra and colleagues, which are widely viewed as fraudulent, are removed from the analyses, no protective effects were seen with exclusive breastfeeding. A large international cross-sectional study published since this review involving 51 119 children in 21 countries also found no protective effect of exclusive breastfeeding for the first 4 months of life on eczema development [30]. Additional observational cohort studies published since the Yang *et al.* review have had mixed results, with six studies showing an *increased* risk of atopic dermatitis in breastfed babies [31–36], one showing a modest protective effect only in a subset of mothers [37], and one showing no effect [38]. A tendency for families with allergy to breastfeed longer may explain the increased risk of atopic dermatitis with prolonged breastfeeding (reverse causation) [35].

#### Drawbacks

There are rare clinical situations where breastfeeding is not recommended – the metabolic condition galactosemia in the neonate, a mother with active untreated tuberculosis, maternal HIV infection, or maternal illicit drug use. In underdeveloped countries, the nutritional and immune benefits of breastfeeding a child of an HIV-infected mother may outweigh the risks of the child contracting HIV [39].

#### Comment

Studies of breastfeeding are observational in nature, as it would be unethical to perform RCTs. Therefore, recommendations cannot be

made on the highest level of evidence, and results of observational studies will always be subject to bias and confounding.

### Implications for clinical practice [clinical evidence category: unknown effectiveness]

Exclusive breastfeeding does not appear to significantly protect a child from the development of atopic dermatitis. Exclusive breastfeeding should be encouraged for the first 6 months of life, as recommended by the World Health Organization and the American Academy of Pediatrics, because of the multitude of beneficial health effects for the infant and mother [39,40]. A recent Cochrane review also concluded that the optimal duration of exclusive breastfeeding in both developed and undeveloped countries is 6 months [41].

### Can restricting the maternal diet during pregnancy or lactation prevent atopic dermatitis?

Children with atopic dermatitis have an increased risk of allergic sensitization, although the role of IgE sensitization in eczema development is unclear. Maternal dietary antigens are able to cross the placenta and can be found in breast milk. Thus, reducing exposure of these antigens to the fetus or infant was thought to reduce the chance of sensitization and possibly atopic dermatitis development.

#### Efficacy

A Cochrane systematic review (good quality) by Kramer and Kakuma, which was updated in 2012, reviewed five trials with 952 subjects [41]. Meta-analysis of two trials demonstrated no effect of food avoidance during pregnancy on the risk of atopic dermatitis development during the first 18 months of life. A previous version of this Cochrane review reported a statistically significant protective effect of antigen avoidance during *lactation*, but two studies [42,43] that are thought to contain fraudulent data were not included in the updated Cochrane review in 2012. Therefore, the updated review includes only one trial of antigen avoidance during lactation, and this trial found no protective effect.

#### Drawbacks

One trial found a statistically significant lower mean gestational weight gain with maternal dietary restriction [44]. There were statistically weak suggestions that restricting the maternal diet increases the risk of preterm birth and leads to lower birth weight.

#### Comment

There has been little research activity in this field in the past 15 years. The potential harmful effects of restricting the maternal diet will likely dissuade future research using this approach. Restricting antigen exposure is becoming a less attractive strategy given the emerging data, suggesting the potential beneficial effects of early allergen exposure [45].

### Implications for clinical practice [clinical evidence category: likely to be ineffective or harmful]

The maternal diet during pregnancy or lactation should not be restricted to prevent atopic dermatitis.

### Can administration of probiotics to the mother or baby prevent atopic dermatitis in infants and children?

Probiotics are defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the

host” [46]. There has been a great deal of interest over the past decade in the role of probiotics for the treatment and prevention of eczema.

### Efficacy

Several systematic reviews have been published since 2007 of trials comparing probiotics with placebo for the prevention of eczema, including a Cochrane review [20,47–49], all suggesting that probiotics can reduce the risk of developing eczema; however, there were areas of weakness in the methodology of some of these reviews, such as missing trials and the inclusion of the same trial population more than once in the meta-analyses.

We identified a high-quality comprehensive systematic review published in 2012 [50] that included 13 double-blind placebo-controlled RCTs of probiotics for the prevention of eczema. All but two of these trials included infants at high risk of developing eczema based on family history of atopic disease. Results of the meta-analysis showed that probiotics can significantly reduce the risk of developing eczema compared with placebo by about 20% (relative risk [RR], 0.79; 95% confidence interval [CI], 0.71–0.90). Of the 10 trials that reported IgE-associated eczema, meta-analysis showed a similar reduction (RR, 0.80; 95% CI, 0.66–0.96). We found only one RCT that had been published since this systematic review [51] that also showed a protective effect of probiotics. In this three-arm trial, mothers received one of two probiotic combinations or placebo during pregnancy and breastfeeding. The risk of developing eczema was reduced compared with placebo in both the *Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999 group (odds ratio [OR], 0.17; 95% CI, 0.08–0.35) and the *Lactobacillus paracasei* ST11 and *Bifidobacterium longum* BL999 group (OR, 0.16; 95% CI, 0.08–0.35).

There is significant heterogeneity in the intervention between published trials. Only two trials have compared the same probiotic (*Lactobacillus rhamnosus* GG) and treatment regimen (mother and infant), with conflicting results [52,53]. The Kalliomäki trial of 159 infants showed that, at 2 years old, the rate of eczema was halved in the probiotic group compared with the placebo group (RR, 0.51; 95% CI, 0.32–0.84) [52]; however, Kopp *et al.* tried to replicate this finding in a trial of 105 infants and found no statistically significant difference in the rate of eczema between the two treatment groups (RR, 1.19; 95% CI, 0.68–2.09) [53].

In addition to probiotic strain variability, the recipients of the intervention varied across studies. Providing probiotics to the mother alone appears to be sufficient for a protective effect, although the theoretical protective mechanisms at work in this scenario are more difficult to explain. Subgroup analysis reported in the Pelucchi review showed a similar reduction in the rate of developing eczema, regardless of whether the mother and/or the infant received the intervention. Similarly, a review by Doege *et al.* in 2012, which only included trials that gave the probiotics to the mother and not directly to the infant, showed a similar benefit (RR, 0.82; 95% CI, 0.71–0.95) [54]. A review published in 2011 [55] only included trials of probiotic- and/or prebiotic-supplemented infant formula and concluded that there are currently insufficient data to recommend their routine use.

Further subgroup analyses by Pelucchi *et al.* examining the timing of the intervention (i.e., pre- and/or post-delivery), duration of intervention (more or less than 9 months), dose, and number of probiotic strains given showed no meaningful differences [50]. However, a subgroup analysis of different risk levels of developing eczema suggested that probiotics were more effective in preventing

eczema in infants and children with no family history of allergic disease than those at higher risk, although his meta-analysis was limited to only two trials.

### Drawbacks

The Cochrane systematic review looked in detail at the adverse effects [56]. The only significant effect found was an increase in spitting up at 1 month (RR, 1.88; 95% CI, 1.03–3.45) and 2 months of age (RR, 1.69; 95% CI, 1.02–2.80). There have been no reports of severe adverse events in any published RCT, but there is a possibility that it has not been possible to detect more rare events such as septicemia, as they have included only relatively small numbers of participants.

### Comments

It appears that probiotics can reduce the risk of developing eczema or IgE-associated eczema by about 20%, but translating this finding into practice is difficult because of the variation between trials seen in the intervention and its delivery. Between the 15 trials included here, 10 strains of *Lactobacillus* and eight strains of *Bifidobacterium* were used. In addition, seven trials gave probiotics to the mother and the baby, two to the mother only, and four to the infant only, and the duration of treatment between trials ranged from only 4 weeks up to 2 years. The only attempt to replicate a finding of one trial by using the same probiotic strain and method of administration had conflicting results. This heterogeneity makes it impossible to recommend any one treatment regimen; in fact, the SIGN guidelines on Management of Atopic Eczema in Primary Care concluded that, owing to heterogeneity in patient groups, outcomes, and probiotic strain, no recommendations could be made [21].

Future trials should attempt to replicate previous findings and establish a treatment regimen that is effective and acceptable to parents. Studies on the mechanism of action may help determine what the optimum method of administration should be. The majority of trials conducted so far have been in a high-risk population, so more trials in an unselected population are required to know whether this intervention should be recommended for the general population. Future trials should also assess the effect of probiotics on the severity and the time to onset of eczema.

### Implications for clinical practice [clinical evidence category: likely to be beneficial]

Of all the interventions studies for preventing eczema, the data on probiotics provide the best evidence of benefit, but owing to variations in the intervention used between trials, it is difficult for recommendations to be made for any one treatment regimen.

### Should fatty acid supplementation be given to mothers and neonates to prevent atopic dermatitis?

Epidemiological data support the notion that diets rich in certain omega fatty acids may have several health benefits. Omega fatty acids, especially omega-3 fatty acids, have anti-inflammatory properties. There are some observational data suggesting diets rich in omega-3 fatty acids protect against the development of atopic dermatitis. For these reasons, the role of essential fatty acids in the prevention of atopic dermatitis has been studied; namely, omega-3 and omega-6 fatty acids. These are found in high concentrations in fish and other oils.

## Efficacy

We found one high-quality systematic review on this topic. A further six RCTs were identified that had been published since this review.

The systematic review included five double-blind RCTs that evaluated the effect of omega-3 and -6 oils on the risk of developing eczema [57]. Four of the trials included only high-risk infants [58], with only one including both high- and low-risk infants [59]. Some trials gave the supplement to the mother during pregnancy or breastfeeding [59,60] and others to the infant [58,61] while still others gave the supplement to *either* the breastfeeding mother or to the infant [62]. Meta-analysis showed no effect of the supplementation; three trials of omega-3 supplementation showed a nonsignificant increase in eczema risk (RR, 1.10; 95% CI, 0.78–1.54), whereas meta-analysis of two trials with omega-6 showed a nonsignificant decreased risk (RR, 0.80; 95% CI, 0.56–1.16). Two trials reported a reduction in severity of eczema. Dunstan *et al.* showed those in the omega-3 group were 10 times less likely to develop severe eczema (OR, 0.09; 95% CI, 0.01–0.94) [60]. Van Gool *et al.* showed a decreased SCORAD in the omega-6 group (mean plus/minus standard deviation [SD],  $6.32 \pm 5.32$ ) compared with the control group (mean  $\pm$  SD,  $8.28 \pm 6.54$ ) [58].

An RCT published in 2009 randomized 145 pregnant women to receive either omega-3 supplementation or placebo during late pregnancy and while breastfeeding [63]. The study showed a statistically significant reduction in IgE-associated eczema at 12 months (4/52 vs 15/63;  $P = 0.02$ ). When these high-risk infants were followed up at 2 years of age, a statistically significant reduction in the cumulative incidence of IgE-associated eczema remained (5/54 vs 15/63;  $P = 0.04$ ), but no difference was seen in the incidence of “any eczema” [64].

In another RCT, Linnamaa *et al.* gave blackcurrant seed oil, which is rich in omega-3 and -6 fatty acids, or placebo to 322 mothers during pregnancy and while breastfeeding, as well as to the infants up to 2 years of age [65]. There was a statistically significant reduction in the number of children with eczema at 1 year of age (33% vs 47.3%;  $P = 0.035$ ), but this significance was lost by 2 years of age (38.8% vs 48.9%;  $P = 0.18$ ).

In another high-risk population, Palmer *et al.* randomized 706 mothers to receive fish oil or placebo during pregnancy [66]. They observed a significant reduction in the number of infants with IgE-associated eczema at 1 year of age (RR, 0.61; 95% CI, 0.38–0.98). In contrast, D’Vaz *et al.* randomized 420 high-risk infants to receive daily fish oil supplement or placebo until the age of 6 months [67]. At 12 months they were assessed for eczema and found no difference between the two groups.

Lastly, in an RCT published in 2012, the authors used dietary advice to supplement with essential fatty acids [68]. They randomized 123 mothers to advice to consume oily fish (salmon) twice a week or continue with their existing diet during pregnancy. Eighty-six infants were assessed at 6 months for eczema and no significant difference between the two groups was found in the incidence of eczema (25.0% vs 18.4%;  $P = 0.46$ ) or the severity (mean  $\pm$  SD,  $7.4 \pm 3.5$  vs  $10.0 \pm 8.9$ ;  $P = 0.37$ ).

## Drawbacks

While it could be assumed that essential fatty acids would not have an adverse effect, none of the trials reported on safety. Recent studies reveal n-6 omega fatty acids could have a pro-carcinogenic effect [69].

## Comments

There are a number of good-quality RCTs on this topic, but the conclusions drawn differ between trials. The systematic review suggested that omega-3 and -6 fatty acids are not an effective intervention for preventing eczema, but several RCTs have been published since this review, some of which suggest there may be a preventative effect. Additionally, there is variation in the intervention between trials; in some, the supplement is given to the mother, in others the infant, and in others to the mother and the infant [62]. This may explain some of the differences observed, because most of the RCTs reported were conducted in high-risk infants, so it is unclear how these findings would translate to the wider population.

## Implications for clinical practice [clinical evidence category: unknown effectiveness]

The intervention varies between trials and the results of the trials are variable, so it is difficult to make firm recommendations for clinical practice.

## Should the introduction of complementary foods to the infant be delayed to prevent the development of atopic dermatitis?

Reducing exposure to food allergens early in life was thought to prevent IgE sensitization despite a paucity of supporting data. By reducing food sensitization, researchers hoped to reduce the risk of atopic dermatitis development. Recent data suggest that delaying exposure to food antigens may actually *increase* the risk of IgE sensitization. There may be a window of opportunity during infant development for the induction of immune tolerance via oral exposure [70].

## Efficacy

There were no systematic reviews of RCTs or individual RCTs available for review. A systematic review (moderate quality) of nine observational studies reporting on six cohorts by Tarini *et al.* published in 2006 concluded that the early introduction of solid food before 4 months of age *may* increase the risk of eczema development [71]. Tarini *et al.* also commented that the majority of studies were poorly designed and were susceptible to bias. Since the Tarini *et al.* review, four observational studies have been reported, with three of these showing a *reduced* incidence of atopic dermatitis with early introduction of solid food [37,72,73] and one showing no effect [74].

## Drawbacks

The question of delaying the introduction of solid food is likely more relevant to the development of food allergy than to atopic dermatitis development. Delaying the introduction of solid food may actually *increase* the risk of food allergy. Emerging data reveal early oral exposure to food allergens may induce tolerance [70]. Previous guidelines by the American Academy of Pediatrics and the UK Health Service recommending the strict avoidance of allergenic foods until 1–3 years of age were not based on robust data and these recommendations have since been retracted [29,41].

## Comment

Despite previous recommendations to the contrary, delaying the introduction of solid foods beyond 6 months does not prevent atopic dermatitis and may increase the risk of food allergy. The best approach for introducing allergenic foods (e.g., peanut, egg, soy, fish) for children with atopic risk factors is not known. The Learning



Early About Peanut Allergy study ([www.leapstudy.co.uk](http://www.leapstudy.co.uk)) and the Enquiring About Tolerance study ([www.eatstudy.co.uk](http://www.eatstudy.co.uk)) are two large ongoing RCTs examining whether early introduction of allergenic foods protects or promotes atopic dermatitis and food allergy. Initial results are expected in 2014.

### **Implications for clinical practice [clinical evidence category: likely to be ineffective or harmful]**

Parents should be instructed to gradually introduce foods beginning around 6 months of age. Although no data are available to guide food introduction in children with a family history of atopic disease (i.e., high risk), it would be prudent to introduce allergenic foods in small volumes one at a time, at a minimum of 4-day intervals. Foods should be given at home with antihistamines available [75]. Immediate medical care should be sought if symptoms of immediate hypersensitivity are observed. The Food Standards Agency in the UK recommends seeking counsel with a health-care provider prior to introducing peanut protein in children with a first-degree relative with atopic disease [76].

### **If exclusive breastfeeding is not possible, should a hydrolyzed formula be used to prevent atopic dermatitis in high-risk infants?**

Hydrolyzed formulas are thought to reduce the risk of IgE sensitization to milk protein in at-risk neonates. The food allergy guidelines published by the National Institutes of Health in 2010 found only a moderate level of evidence that hydrolyzed formulas can reduce cow milk sensitization in high-risk neonates, but found they do not have an effect on the sensitization to other food antigens. The relationship between cow milk sensitization and the development of atopic dermatitis is unclear.

### **Efficacy**

Four recent systematic reviews and one government-sponsored health claim review were identified that evaluated the role of hydrolyzed formulas in atopic dermatitis prevention [77–81]. The Cochrane review (high quality) found no statistically significant effect of hydrolyzed formula compared with cow's milk formula with the exception of a subgroup analysis of three studies of extensively hydrolyzed casein formula. Osborn and Sinn [77] concluded that, owing to "methodological concerns," better RCTs are needed. A systematic review published in 2010 by Alexander *et al.* [78] (moderate quality), which was partially funded by the Nestle Corporation, found the use of *partially* hydrolyzed whey protein formula reduced the incidence of atopic dermatitis compared with standard cow milk formula. A systematic review by Szajewska and Horvath [80] (moderate quality) published in 2010, also funded by Nestle, found a protective effect of *partially* hydrolyzed whey formula on atopic dermatitis development. Szajewska and Horvath's review only included studies that used formulas manufactured by Nestle, however. The US Food and Drug Administration (FDA) undertook a qualitative assessment of all systematic reviews and meta-analyses to evaluate a "qualified health claim" proposal by Nestle in 2011. They concluded that "there is little to very little credible evidence for a qualified health claim about W-PHF [partially hydrolyzed whey formula] and a reduced risk of AD [atopic dermatitis]," although the FDA *did* accept a qualified health claim for the product [82]. Since the publication of these reviews, a randomized controlled study of 620 high-risk infants was reported by Lowe *et al.*, who found no reduction in the incidence of eczema or

any atopic disease at 2 years with the use of partially hydrolyzed whey formula or soy formula [82].

### **Drawbacks**

Potential drawbacks of the use of hydrolyzed formulas include the incorrect perception of hypoallergenicity, potential adverse effects on growth, poor palatability, and cost. A significant percentage (up to 50%) of infants with true milk allergy experience allergic reactions to partially hydrolyzed whey formulas [83–85]. Some studies involving preterm infants have shown reduced growth rates with the use of hydrolyzed formulas [86,87], although these effects have not been seen in term infants. Issues with palatability and compliance with hydrolyzed formulas have been reported [88–90]. The cost of *extensively hydrolyzed* formulas is also significantly more than standard cow milk formula, although the use of *partially hydrolyzed* whey formula showed a cost benefit in atopic dermatitis prevention in at least one study [91].

### **Comment**

The conflicting results and conclusions of the reviews result primarily from differences in how studies were selected for inclusion. For example, Osborn and Sinn excluded a study by Chan showing positive effects of a hydrolyzed formula because of excess loss to follow-up, while Alexander *et al.* included this study in the analysis. The two largest, most recent, and best-reported RCTs have conflicting results [82,92]. The German Infant Nutritional Intervention study, the highest quality RCT performed to date, found upon intent-to-treat analysis that the use of partially hydrolyzed whey formula had a significant effect on eczema prevention, but paradoxically did not see a protective effect for the extensively hydrolyzed whey formula. The RCT by Lowe *et al.* did not find a protective effect of partially hydrolyzed whey formula [82].

### **Implications for clinical practice [clinical evidence category: unknown effectiveness]**

There is some evidence supporting the use of a partially hydrolyzed whey formula for the primary prevention of atopic dermatitis in high-risk infants. This approach can be considered for infants when exclusive breastfeeding is not possible in the first 6 months of life. Given the significant cost, poor palatability, and inconsistency of the data, the use of extensively hydrolyzed formula cannot be recommended for atopic dermatitis prevention at this time.

### **Should dust mite avoidance measures be used to prevent the development of atopic dermatitis?**

Several studies have shown patients with atopic dermatitis are commonly sensitized to house dust mite and have more dust mites in their environment compared with controls. In contrast, the only prospective cohort study of >500 newborns found *no correlation* between house dust mite antigen exposures and atopic dermatitis development [93].

### **Efficacy**

No systematic reviews were identified. Our search yielded five prospective trials addressing the utility of dust mite avoidance in the primary prevention of atopic dermatitis in infants with a family history of atopy. Three trials looked at dust mite avoidance strategies alone, while two evaluated a multifaceted approach of dust mite avoidance combined with a hypoallergenic diet.

The largest trial ( $n = 721$ ) compared the use of mite-impermeable mattress covers starting at the third trimester on the parents' and



infant's beds against cotton (placebo) covers in a double-blind fashion [94]. Overall, there was a slight trend toward an *increased* risk of atopic dermatitis by history (RR, 1.05; 95% CI, 0.86–1.29) in patients using mite-impermeable covers, a difference that was statistically significant at the last time point.

An unblinded study ( $n = 516$ ) comparing dust-mite-impermeable mattress covers, acaricide use, and supplying a washable play mat with a no intervention control group also demonstrated a significantly *increased* risk of atopic dermatitis by physical exam (20.6% vs 13.7%;  $P = 0.03$ ) and by a questionnaire (33.5% vs 25.3%;  $P = 0.04$ ) at 18 months [95]. At 5-year follow-up, current atopic dermatitis (25.7% vs 18.5%;  $P = 0.06$ ) and a history of physician-diagnosed eczema (34.8% vs 23.9%;  $P = 0.009$ ) remained more common in the intervention group [61]. A small study ( $n = 251$ ) comparing mattress covers, acaricides, and vinyl flooring against no intervention found a similar prevalence of atopic dermatitis at 1 year in the intervention and control groups (40% vs 37%;  $P$  value not reported) [96].

The smallest study identified ( $n = 120$ ) evaluated the use of mattress covers, acaricides, and a restrictive diet where the breastfeeding mother and infant were asked to avoid foods containing dairy, egg, wheat, nuts, fish, and soy for the first 12 months of life, compared with a non-intervention control group [97]. At 8-year follow-up, there was a trend toward a decreased risk of atopic dermatitis in the intervention group (36.2% vs 46.8%;  $P = 0.16$ ), which achieved statistical significance when the data were adjusted for multiple confounders (OR, 0.23;  $P = 0.005$ ). These results were not replicated in a larger study ( $n = 696$ ) comparing the use of mattress covers and a book explaining allergen avoidance measures (exclusive breastfeeding or use of a hypoallergenic formula until 3 months, avoidance of wheat and cow's milk until 6 months, avoidance of egg and fish until 12 months, avoidance of peanuts and tree nuts until 3 years, removal of carpets from the infant's room, and weekly vacuuming), against a group given a control booklet [98]. The risk of physician diagnosis of eczema was similar in the intervention and control groups (18.8% vs 21.1%;  $P = 0.516$ ).

### Drawbacks

Dust-mite-impermeable mattress covers are relatively innocuous, although the studies by Gehring's and Mihrshahi's groups do raise the possibility of dust mite avoidance potentially promoting the development of atopic dermatitis.

### Comment

Overall, the studies were relevant to this clinical question, adequately powered and of relatively good quality, including one large double-blind, placebo-controlled trial. Although there was an opportunity for bias in the unblinded trials, one would expect this to skew the results to show a protective effect of dust mite avoidance strategies, which was generally not present. Rather, there was a significantly increased risk of atopic dermatitis by some measures in two large studies, compared with a significantly decreased risk in the adjusted data of the smallest study.

### Implications for clinical practice [clinical evidence category: likely to be ineffective or harmful]

Although one small study has shown some benefit of dust mite avoidance in the prevention of atopic dermatitis, larger studies and one double-blinded, placebo-controlled trial have shown them to increase the risk of atopic dermatitis development or to not be helpful. Dust mite avoidance measures should not be recommended for the primary prevention of atopic dermatitis.

## Does early emollient use prevent the development of atopic dermatitis?

There is increasing evidence that the primary event in the development of eczema is a defective epidermal barrier, which allows allergens and irritants to enter the body and trigger the inflammatory response [99]. Therefore, it is logical to consider whether regular application of emollient from birth may enhance the skin barrier sufficiently to prevent eczema from developing.

### Efficacy

Despite their widespread use in *treating* eczema, there is very little published evidence on the role of emollient therapy in *preventing* eczema. We found no published systematic reviews on the role of emollients for the prevention of eczema. We did identify two small pilot RCTs (both published in abstract form only), one open-label prospective study and one case-control study that looked at simple emollients for the prevention of eczema.

A pilot RCT carried out in the UK and the USA by Simpson *et al.* randomised 124 newborn infants at high risk of atopic disease to receive either daily emollient plus skin care advice or skin care advice alone [14]. An intention-to-treat analysis of the 6-month cumulative incidence of a blinded assessment of eczema status showed a reduction in the rate of eczema in the emollient group; the OR of developing eczema in the emollient group compared with the control group was 0.37 (95% CI, 0.14–0.91;  $P = 0.017$ ). Conversely, a second small pilot RCT conducted in Japan that randomized 71 babies at high risk of atopic disease to either emollients plus instructions on skin care or control found no difference between the two groups in the rate of eczema during the first 6 months of life in a per-protocol analysis [100]. However, they did show that there were fewer children with positive reaction to skin prick tests in the emollient group. In a prospective open-label pilot study by Simpson *et al.*, 22 babies at high risk of developing eczema were enrolled [101]. Parents were instructed to apply a petrolatum-based cream to their infant at least once a day and the mean follow-up time was 547 days. The proportion of children developing eczema was 15%, which is between 15 and 35% lower than expected in this high-risk group, suggesting a protective effect of the emollient. A case-control study published in 1991 including 54 Kenyan children with eczema and 63 matched controls [102] found that the odds of developing eczema were reduced by application of petrolatum in early life (OR, 0.33; 95% CI, 0.14–0.80).

### Drawbacks

Although there is a lack of evidence regarding safety, it is unlikely that emollients will cause harm in this setting. Several groups have shown that regular application of emollients can improve the condition of the immature skin of preterm neonates, reduce the amount of dermatitis, and does not result in harmful side effects [103–108]. However, it is possible that occlusion as a result of applying emollients daily from birth could result in adverse effects such as folliculitis and skin infections. A case-control study by Campbell *et al.* found petrolatum use on the skin increased the risk of systemic candidiasis in extremely low birth weight infants [109]. No increase in cutaneous infections or other adverse events occurred in the three trials of emollient therapy for eczema prevention mentioned above, although the pilot RCT by Kataoka and colleagues did not specifically report on the safety of emollients [100].

### Comments

Since the discovery of mutations in the gene encoding FLG, a key skin barrier protein, and the strong association of FLG mutations

with allergic disease [110,111], there has been a great deal of interest in interventions that target the skin barrier to prevent eczema [112]. However, there is currently no high-level evidence on this topic, so there is a need for further RCTs to be conducted. They should be adequately powered to detect a response; those published so far are only small pilot RCTs, which may explain the difference in findings. Additionally, in both these RCTs the infants were only followed up for 6 months; future trials should aim for at least 2 years of follow-up to distinguish eczema from the many eczematous rashes seen in young babies. Trials should also assess the severity and time of onset of eczema to determine whether emollients can reduce the severity or delay the onset. Finally, it is important that trials of existing simple, cheap emollients are carried out, as well as trials of the newer, more state-of-the-art emollients that are now being marketed.

### Implications for clinical practice [clinical evidence category: unknown effectiveness]

There is currently insufficient evidence to recommend the use of emollients to prevent eczema. There is a suggestion that emollients could be effective, but the evidence is weak and more high-quality data regarding the safety and effectiveness of emollients applied daily from birth are needed before any recommendations can be made.

#### Key points

- Despite decades of research, no single strategy has emerged as clearly effective for atopic dermatitis prevention.
- Although the effect is modest (20% reduction), probiotics appear to have the strongest evidence for a protective effect. However, it is difficult to recommend any one strain of probiotic or treatment regimen because of the heterogeneity between trials.
- There is a modest level of evidence to support the use of partially hydrolyzed whey formulas for atopic dermatitis prevention in high-risk infants who are unable to exclusively breastfeed for the first 4–6 months of life.
- Given the conflicting data, omega fatty acid supplementation cannot be strongly recommended for atopic dermatitis prevention.
- Restricting the maternal or infant diet is not protective and should not be recommended.
- Delaying the introduction of solid foods does not prevent atopic dermatitis and theoretically could increase the risk of food allergy development.
- Dust mite avoidance measures should not be recommended for atopic dermatitis prevention.
- Emollients are a promising intervention for preventing eczema, but the evidence available is insufficient to make any recommend their use and there is a need for large RCTs.

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# Atopic eczema

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## Coverage and main data sources

Since over 200 types of interventions belonging to 12 broad categories have been tried in atopic eczema (synonymous with atopic dermatitis), complete coverage of all therapy-related issues for atopic eczema is not possible, even in a chapter of this size. Instead, we have opted to introduce the evidence base for treating atopic eczema by means of three common clinical scenarios:

- Case scenario 24.1: a child with moderately severe atopic eczema.
- Case scenario 24.2: a person with clinically infected atopic eczema.
- Case scenario 24.3: an adult with severe atopic eczema.

Much of the background work and methodology within the sections has been based (with appropriate updates) on the results of a systematic review of eczema treatments funded by the UK National Institute of Health Research (NIHR) Programme Grant for Applied Research, which has resulted in a comprehensive database of all randomized controlled trials (RCTs) of eczema called the Global Resource for Eczema Trials (GREAT) database (<http://www.greatdatabase.org.uk/>). The GREAT database is free for all to access in the public domain and it builds on a previous overarching systematic review of atopic eczema treatments, which was published at the end of 2000 (<http://www.hta.ac.uk/fullmono/mon437.pdf>). Readers are recommended to check with the GREAT database as more RCTs are added in what has now become a rapidly moving field. Additional information on systematic reviews on atopic eczema has been gleaned from a summary mapping exercise of all eczema systematic reviews which has been conducted at the Centre of Evidence-Based Dermatology at the University of Nottingham (<http://www.nottingham.ac.uk/dermatology>).

## Background

### Definition and diagnostic criteria

Atopic eczema (atopic dermatitis) is a chronic inflammatory skin condition characterized by an itchy red rash that favors the skin creases, such as the folds of the elbows, behind the knees, and around the neck. The morphology of the eczema lesions varies in appearance from vesicles and oozing to gross lichenification on a background of poorly demarcated redness. Other features such as

crusting, scaling, cracking, and swelling of the skin can occur [1]. Atopic eczema is associated with other atopic diseases such as hay fever and asthma, although such associations may reflect shared environmental causes, as opposed to genetics. People with atopic eczema also have a tendency to have a dry skin, which increases their vulnerability to the irritant effects of soaps. Much of the dry skin tendency might be secondary to deficiencies in filaggrin protein expression, which is genetically determined and important in white European populations [2,3].

Atopic eczema typically starts in early life, with about 80% of cases starting before 5 years of age [4]. Although the word “atopic” is used when describing atopic eczema, it should be noted populations studies show that anything from 20% to 100% of people with otherwise typical atopic eczema are not atopic as defined by the presence of positive skin-prick test reactions to common environmental allergens or through blood tests that detect specific circulating immunoglobulin E (IgE) antibodies [5,6]. The role of atopy in atopic eczema has been systematically reviewed elsewhere [7]. The word “atopic” in the term “atopic eczema” is simply an indicator of the frequent association with atopy (especially in more severe hospital populations in developed countries) and the need to separate this clinical phenotype from other forms of eczema, such as irritant or allergic contact eczema, which have other causes and distinct patterns. The terms “atopic eczema” and “atopic dermatitis” are synonymous. The term “atopic eczema,” or just “eczema,” is frequently used in the UK, whereas the term “atopic dermatitis” is used more in the USA. Much scientific energy has been wasted in debating which term should be used, culminating in the World Allergy Organization proposal for a revised nomenclature [8].

Very often, no definition of atopic eczema is given in clinical studies such as clinical trials. This leaves the reader guessing as to what sort of people were studied. Atopic eczema is a difficult disease to define, as the clinical features are highly variable with regard to morphology, body site, and time. There is no specific diagnostic test encompassing all people with typical eczema that can serve as a reference standard. The diagnosis is, therefore, essentially a clinical one.

At least 10 synonyms for atopic eczema were in common usage in the dermatology literature in the 1970s, and it is doubtful whether physicians were all referring to the same disease. A major



**Box 24.1**

In order to qualify as having a case of atopic eczema, the person must have an itchy skin condition plus three or more of the following [11]:

- past involvement of the skin creases, such as bends of elbows or behind the knees;
- a personal or immediate family history of asthma or hay fever;
- a tendency towards a generally dry skin;
- onset under the age of 2 years;
- visible flexural dermatitis, as defined by a photographic protocol.

development in describing the main clinical features of atopic eczema was the Hanifin and Rajka diagnostic criteria (1980) [9]. These criteria are frequently cited in clinical trial articles, and they at least provide some degree of confidence that researchers are referring to a similar disease when using these features. It should be borne in mind, however, that these criteria were developed on the basis of consensus based on experience with seeing more severe cases in a hospital setting [5]. Some of the minor features have since been shown not to be associated with atopic eczema, and many of the terms, which are poorly defined, probably mean something only to dermatologists. Scientifically developed refinements of the Hanifin and Rajka diagnostic criteria, mainly for epidemiological studies, have been developed by a UK working party, and these criteria have been widely used throughout the world and in clinical trials (Box 24.1) [10,11]. The UK refinement of the Hanifin and Rajka criteria have been the most widely validated criteria worldwide, as summarized in a systematic review [12].

It is quite possible that there are distinct subsets of atopic eczema – for example, those cases associated with atopy, those forms associated with early wheezing [13], those associated with defective filaggrin expression [2], and patients who have severe disease with recurrent infections. Until the exact genetic and causative agents are known, it is prudent to consider the clinical disease as one condition. Perhaps prespecified sensitivity analyses should be done within clinical trials, if large enough, for those who are thought to represent distinct subsets – for example, those with filaggrin gene mutations, those with severe disease and associated asthma, and those who are definitely atopic with raised circulating IgE to allergens – especially for trials of certain interventions, such as reducing house dust mites or food exclusions, where the presence of prior sensitization might be key [5].

### **Incidence/prevalence**

Atopic eczema is a very common problem. European prevalence studies conducted during the last 10 years suggest an overall prevalence of 15–20% in children aged 7–18 years [14]. Standardized questionnaire data from almost a million children aged 6–7 years and 13–14 years in the International Study of Asthma and Allergies in Childhood suggest that atopic eczema is not just a problem confined to western Europe, with high prevalences being found in many developing cities undergoing rapid demographic change [15]. There is reasonable evidence to suggest that the prevalence of atopic eczema has increased in many countries over the last 10 years, although the reasons for this are unclear [16].

Atopic eczema is more frequent in childhood, especially in the first 5 years of life. One study of 2365 patients in Livingston, Scotland, who were examined by a dermatologist for atopic eczema, suggested that atopic eczema is relatively rare over 40 years of age,

with a 1-year period prevalence of 0.2% [17]. Yet, because there are many more adults than children, they may make up over 38% of all atopic eczema cases in that community. Adults also tend to represent a more persistent and severe subset of cases.

Most cases of childhood eczema in any given community are mild. One study found that 84% of 1760 children aged 1–5 years from four urban and semi-urban family practitioners around Nottingham, England, were mild, as defined globally by the examining physician, with 14% of cases in the moderate category and 2% in the severe category [18] – a severity distribution that was very similar to that in another population survey in Norway [19].

### **Morbidity and costs**

Atopic eczema usually accounts for the worst disturbance in quality of life in comparison with other dermatological diseases. Specific aspects of a child's life affected by atopic eczema are [14]:

- itch and its associated sleep loss (which can also cause considerable family disturbance);
- social stigmatization from other children and parents;
- the need for special clothing and bedding;
- avoidance of activities such as swimming;
- the need for frequent applications of topical treatments and visits to health-care professionals.

In financial terms, the cost of atopic eczema is potentially very large. One study of an entire community in Scotland in 1995 estimated that the annual personal costs to patients with atopic eczema was £297 million (US\$606 million), if extrapolated to the entire UK [20]. The cost to the National Health Service was £125 million, and the annual cost to society through lost working days was £43 million, making the total expenditure on atopic eczema £465 million per year (US\$949 million). This figure is likely to be an underestimate, since the prevalence of atopic eczema is lower in Scotland in comparison with the rest of the UK. Another study from Australia found that the annual personal financial cost of managing mild, moderate, and severe eczema was A\$330, A\$818, and A\$1255, respectively, which was greater than the costs associated with asthma in that study [21]. One systematic review that tried to estimate the national costs of eczema in the USA found four informative studies with annual costs (direct plus indirect) estimated to be between US\$364 million and US\$3.8 billion per year in 2008 [22].

### **Etiology**

#### **Genetics**

There is strong evidence to suggest that genetic factors are important in the predisposition to atopic eczema. Twin studies have shown a much higher concordance for monozygotic (85%) than for dizygotic twins (21%) [23]. Genes coding for filaggrin proteins have been the strongest and most consistent marker of increased eczema risk in several populations [24,25], and such mutations are also associated with more severe and persistent disease and more asthma [26]. Other genes coding for immune response and the ability to deal with *Staphylococcus aureus* may be important [24], and it is possible that the tendency to atopic eczema might be inherited independently from atopy [27].

#### **Environment**

There are several general and specific clues that point strongly to a role of the environment in disease expression [28]. It is difficult to explain the large increase in the prevalence of atopic eczema over the past 30 years in terms of genetics [16]. It has been shown that

atopic eczema is more frequent in wealthy families [29]. It is unclear whether this positive social class gradient reflects exposure to indoor allergens or whether it reflects a whole constellation of other factors associated with social “development.” Other studies have shown an inverse association between the prevalence of eczema and family size [30]. This observation led to the “hygiene hypothesis” – that children in larger families were “protected” from expressing atopy because of frequent exposure to infections [31]. Some evidence for this “protective” effect of infections on atopic eczema has been shown in relation to measles infection [32]. The link between fewer infections (bacterial or helminthic) and increased eczema has been reviewed comprehensively elsewhere [33].

Migrant studies also point strongly to the role of environmental factors in atopic eczema. For example, 14.9% of black Caribbean children living in London develop atopic eczema (according to the UK diagnostic criteria), in comparison with only 5.6% of similar children living in Kingston, Jamaica [34].

Further work has suggested that the tendency to atopy may be programmed at birth and could be related to factors such as maternal age [35]. The observation that many cases of atopic eczema improve spontaneously around puberty is also difficult to explain in genetic terms alone [4]. Specific environmental risk factors for the expression of eczema are still not fully elucidated [36]. Allergic factors such as exposure to house dust mite may be important, but nonallergic factors such as exposure to irritants, bacteria, and hard water may also be equally important [37].

### Pathophysiology

There appears to be a failure to switch off the natural predominance of T-helper 2 lymphocytes that occurs in infancy, which leads to an abnormal response of chemical messengers called cytokines to a variety of stimuli [1,38]. The underlying mechanism of disease may be abnormalities in cyclic nucleotide regulation of marrow-derived cells or allergenic overstimulation, causing secondary abnormalities [39]. Some studies have demonstrated a defect in lipid composition and barrier function in people with atopic eczema – a defect that is thought to underlie the tendency to dry skin and possibly the enhanced penetration of environmental allergens and irritants, leading to chronic inflammation.

### Prognosis

The majority of children with atopic eczema appear to “grow out” of their disease, at least to the point where the condition becomes a problem no longer in need of medical care. A detailed review of prognostic studies reported elsewhere [4] concluded that most large studies of well-defined and representative cases suggest that about 60% of childhood patients are clear or free of disease symptoms in early adolescence. However, many such apparently clear cases are likely to recur in adulthood, often as hand eczema. The most consistent factors that appear to predict persistent atopic eczema are early onset, severe widespread disease in infancy, concomitant asthma or hay fever, and a family history of atopic eczema. One birth cohort study of 1314 children followed to age 7 years in Germany (The Multicenter Allergy Study) found that of the 21.5% of children with eczema in the first 2 years of life, 43.2% were in remission by age 3 years, 38.3% had intermittent disease, and 18.7% had symptoms every year. Poor prognosis was related to IgE sensitization and early disease severity. Early eczema without early wheezing did not increase the risk of subsequent wheeze at school entry age (adjusted odds ratio, 1.11; 95% confidence interval [CI], 0.56–2.20) [13].

### Aims of treatment

Cure is an unrealistic option for the majority of sufferers, as it is so unusual for there to be a single, treatable cause for atopic eczema, such as a specific food allergy. In addition, the effect of conventional treatment on the long-term natural history of the disease is simply not known. Treatment is thus aimed at relieving troublesome symptoms such as itch and soreness and its associated sleep loss, in order to improve the person's quality of life. Improvement in skin appearance may also be important, as is self-esteem, social confidence, and the ability to participate freely in recreational activities such as swimming. In addition to short-term relief of symptoms, recent interest has focused on disease modification strategies and prevention of flares as part of proactive long-term control which are discussed later in this chapter [40,41].

### Relevant outcomes

Outcome measures used in trials have been reviewed by Finlay [42]. Most outcome measures have incorporated some measure of itch, as assessed by a doctor at periodic reviews or patient self-completed diaries. Other more sophisticated methods of objectively recording itch have been tried. Finlay drew attention to the profusion of composite scales used in evaluating atopic eczema outcomes. These usually incorporate measures of the extent of atopic eczema and several physical signs, such as redness, scratch marks, thickening of the skin, scaling, and dryness. Such signs are typically mixed with symptoms of sleep loss and itching, and variable weighting systems are used. It has been shown that measuring surface area involvement in atopic eczema is fraught with difficulty [43] – which is not surprising, considering that eczema is, by definition, “poorly defined erythema.” Charman and Williams carried out a systematic review of named outcome measure scales for atopic eczema and found that of the 13 named scales in current use, only one (scoring atopic dermatitis, SCORAD) had been fully tested for validity, repeatability, and responsiveness [44]. A further systematic review of 20 named scales used to measure eczema severity found that only three – SCORAD, eczema area and severity index (EASI), and patient-orientated eczema measure (POEM) – had been tested sufficiently and performed adequately when tested [45]. Quality-of-life measures specific to dermatology include the dermatology quality of life index [46] and Skindex [47]. The children's dermatology life quality index (CDLQI) has been used in atopic eczema trials in children. Subsequent work by Charman *et al.* has resulted in the development of the patient-oriented outcome measure known as POEM – an outcome that measures items that are deemed to be important for patients and which can also be used for rapid monitoring in routine clinical practice [48].

Most clinical trials of atopic eczema have been very short (i.e., about 6 weeks), which seems inappropriate in a chronic relapsing condition [49]. Few studies have considered measuring the number and duration of disease-free periods, apart from a few exceptions in the use of topical calcineurin inhibitors and “weekend” treatment for topical corticosteroids. In the absence of such long-term studies, it is impossible to say whether modern treatments have increased chronicity at the expense of short-term control. The definition of a “flare” of atopic eczema is problematic and has been reviewed by Langan *et al.*, who also propose a series of long-term outcomes such as the number of “well-controlled weeks,” analogous to long-term asthma outcomes [50]. As a result of the profusion of outcomes in eczema and inappropriate emphasis on short-term changes, an international group called the Harmonizing Outcome Measures for Eczema (HOME, <http://www.homeforeczema.org/>)

group has formed to try to define a short list of core outcome sets that should be used in all future atopic eczema trials. Early work using an international Delphi process has identified four domains, including symptoms, signs, long-term disease control, and quality of life [51].

## Questions

### Case scenario 24.1: a child with atopic eczema of moderate severity

Figure 24.1 shows a child with atopic eczema.

#### What is the role of emollients?

##### *Efficacy*

Current clinical guidelines recommend “complete emollient care” including leave-on emollients, soap substitutes and bath emollients [52,53]. Despite limited evidence for any of these products, clinical opinion is generally supportive of the liberal use of emollient therapy for the management of eczema.

Since the last edition of this book, there has been renewed interest in the topic of emollient therapy for eczema and we identified 33 RCTs that included emollient therapy as either the active or the control intervention. Further details of these trials are summarized in Web Table 24.1. Overall, five of the trials compared emollients with no emollients [54–58]; 16 compared one emollient with another [59–74]; 10 trials compared emollients with topical corticosteroids or calcineurin inhibitors [75–84]; and two trials compared emollients with other active eczema treatments [85,86]. Trials on the use of bath emollients are discussed in the section on washing and bathing.

A particular focus of recent studies has been on the potential steroid sparing capabilities of emollients, where two reasonably large studies ( $n = 173$  and  $n = 162$  respectively) comparing emollient therapy with no emollient therapy have suggested possible steroid-sparing effects, with no apparent increase in eczema severity [55,56].

Three studies have looked at the use of maintenance therapy and the role of emollients in preventing eczema flares. One trial compared maintenance therapy with topical corticosteroid plus emollients against emollient therapy alone (control), and a second

compared maintenance with a calcineurin inhibitor (tacrolimus 0.03% or 0.1%) against emollient therapy alone [78,84]. Both of these trials favored active treatment compared with emollients alone and are discussed further in the sections on topical corticosteroids and calcineurin inhibitors. A third trial looked explicitly at the ability of emollients to prevent eczema flares in 44 adults with eczema [57]. In this parallel group RCT, emollient therapy (Canoderm® cream) was applied to a single site twice daily until relapse (or until the end of 6 months), compared with no use of emollients at a target site. Median time to relapse for the emollient group was over 180 days (length of the study) compared with 30 days in the no-emollient group. The proportion of participants who remained eczema free for the entire 6-month maintenance phase was 68% in the emollient group and 32% in the no-emollient group.

##### *Drawbacks*

Adverse effects from emollients are generally poorly reported in clinical trials, although most side effects that have been reported were mild (including transient burning), or relate to cosmetic acceptability.

There are currently many brands of emollients available, and new, expensive “barrier-enhancing” products are emerging. Whether the additional cost of these products is warranted compared with simpler and relatively cheap alternatives remains to be seen, and large pragmatic studies are required to establish the relative cost effectiveness of different products.

##### *Comments*

Whilst it is pleasing to see the number of emollient trials expanding, the lack of reporting of methodological detail and the seeming lack of regard for addressing the most clinically pressing issues is disappointing. It is questionable whether testing emollients in RCTs is needed and ethical given that they are so deeply engrained in medical practice. Some may argue that the point of equipoise has passed. Yet, given that some emollients such as aqueous cream may actually cause harm [87], it is important to recognize that some products may be more beneficial than others, and that a range of products may be needed for different parts of the body and for different skin types and ages.

The effects of emollients as part of a package of care are difficult to assess, and need to be long term in order to pick out any possible subtle benefits such as prevention of flares. The current body of evidence does appear to support the use of emollients in the management of eczema, and lends weight to the suggestion that it does not necessarily matter which emollient you choose as long as one is used.

Future research into which emollients are best, how much emollient to use, when to apply it, and how best to ensure adherence with topical medications is now warranted.

##### *Implications for clinical practice*

There is currently no evidence to doubt the belief that regular emollient use is beneficial for the treatment of the dry skin associated with atopic eczema, and there is some evidence to suggest that regular emollient use can prevent eczema flares and reduce the amount of topical steroid needed. Given the huge variety of emollients currently available and the widely varying costs, further research would be helpful to establish which products are most cost effective and most acceptable to patients.



Figure 24.1 A child with atopic eczema.



**Key points: emollients**

- Thirty three RCTs have been summarized. Five trials compared emollient therapy with no emollients, 16 compared one emollient with another, 10 trials compared emollients with topical corticosteroids or calcineurin inhibitors, and two trials compared emollients with other active eczema treatments.
- There is some evidence to suggest that emollients may be steroid sparing and that they can be useful in the prevention of eczema flares.
- The paucity of good clinical trial evidence does not reflect the importance of emollient therapy for the treatment of atopic eczema.

**Do topical steroids help?****Efficacy**

**Versus placebo** The effectiveness of topical corticosteroids in comparison with placebo has been demonstrated in one systematic review (search date 1999, 13 RCTs) [49] and nine further RCTs [76,88–94] comparing topical steroids with placebo (vehicle) applied for up to 6 weeks in patients with atopic eczema (Web Table 24.2). Nineteen studies found significant improvement with topical steroid in comparison with placebo [76,89–104]. Hebert *et al.* and Lebwohl each include two RCTs [94,102] (Web Table 24.1). The three remaining studies were unable to demonstrate a significant difference between steroid and placebo [88,105,106]. No long-term studies were identified.

**Versus each other** One systematic review (including 40 RCTs) [49] and four further RCTs (including 539 patients) were identified that compare a variety of topical steroids with each other (Kirkup *et al.* [107] include two RCTs) [76,107,108]. These studies showed significant improvements in 13–100% of patients after 1–12 weeks of treatment.

**Versus topical tacrolimus and pimecrolimus** This is discussed in later sections of this chapter.

**Prevention of relapse** Five RCTs have demonstrated that intermittent treatment with a potent topical steroid can reduce the number of flare-ups of atopic eczema [78,109–112]. In the first three RCTs, adults ( $n = 430$ ) or children aged 4–10 years ( $n = 90$ ) with atopic eczema were stabilized with a 4-week course of a potent topical steroid (fluticasone propionate), followed by subsequent application of the steroid on two consecutive days a week for 16 weeks. “Weekend” steroid therapy was significantly more effective in maintaining an improvement in comparison with placebo [109,110,112]. In the fourth RCT (including 372 adults and children), patients were stabilized with a 4-week course of fluticasone propionate followed by subsequent application on 4 days a week for 4 weeks and then on two consecutive days a week for 16 weeks, again showing a significant reduction in the relapse rate in comparison with placebo [111]. In the fifth RCT patients  $\geq 12$  years ( $n = 249$ ) with atopic eczema were stabilized with a 4-week course of a potent topical steroid (methylprednisolone aceponate 0.1%), followed by subsequent application of the steroid on two consecutive days a week for 16 weeks. “Weekend” steroid therapy was again found to be significantly more effective in maintaining an improvement in comparison with placebo [78]. No direct comparisons of relapse prevention by using topical corticosteroids compared with topical tacrolimus or pimecrolimus have been made, although a systematic

review of both treatments used in such a proactive way suggested a larger benefit from topical corticosteroids [41].

**Application under wet wraps** Three RCTs [113–115] and two further small randomized within-patient comparison studies [116,117] have examined the use of wet-wrap bandaging (wet cotton tubular dressings) applied over topical steroids. In the first RCT, 40 children (aged 1–15 years) with moderate to severe eczema were treated once daily with either one-tenth strength mometasone furoate 0.005% ointment or one-tenth strength fluticasone propionate 0.005% ointment unoccluded for 2 weeks, and then randomly assigned to receive the same treatment with or without wet-wrap bandaging for a further 2 weeks. Patients treated with wet wraps finished the study with significantly less extensive and less severe disease, and with a significant improvement in subjective scores [113]. In the second RCT, 50 infants (aged 4–27 months) with moderate to severe eczema were treated with emollients and 1% hydrocortisone, with or without additional wet-wrap bandages, for 4 weeks. In both groups, there was a greater than 50% improvement in the overall eczema score (SCORAD), with no statistically significant differences between the two groups, although the group receiving wet wraps suffered more skin infections [114]. The third RCT was a small randomized controlled pilot study (19 infants <5 years), which found no benefit with 1% hydrocortisone plus wet wraps versus 1% hydrocortisone alone after 2 weeks [115]. In the first within-patient comparison study, 20 children (aged 2–17 years) were treated with twice-daily wet wraps over 0.1% mometasone furoate or vehicle for 5 days (left–right design), with a statistically significant improvement in the side treated with steroid plus wet wraps versus vehicle plus wet wraps [116]. In the second within-patient comparison study, 24 adults and children with an acute exacerbation of eczema were treated with prednicarbate with or without wet wraps (left–right design) for up to 3 days. This study showed a significantly greater improvement on the side treated with topical steroid and wet wraps in comparison with topical steroid alone [117].

A recent critical literature review of the use of wet wraps in children includes nine additional observational studies on the use of wet-wrap dressings in children with atopic eczema; it concluded that large prospective RCTs evaluating wet wraps are lacking [118].

**Frequency of application**

One systematic review (including 10 RCTs and one earlier systematic review [49]), and two further RCTs [92,119] have addressed this issue [120]. These studies found no clear evidence to support twice-daily over once-daily administration of topical corticosteroids, suggesting once-daily treatment as a first step in all patients with atopic eczema.

**Pulsed or continuous treatment**

One RCT (207 children with mild to moderate atopic dermatitis, aged 1–15 years) has compared 3-day bursts of a potent topical steroid (betamethasone valerate 0.1% ointment) followed by a 4-day rest period versus continuous use of a mild preparation (hydrocortisone 1% ointment) for 7 days. Participants used the preparations as required over an 18-week trial period. No significant differences in patient symptoms or clinical disease severity were demonstrated between the two treatment groups [121]. Another RCT study including 40 children (published in abstract form) concluded that pulsed clobetasone butyrate 0.05% is more effective than continuous treatment [122].

### Drawbacks

No serious systemic effects or cases of skin atrophy were reported in the short-term RCTs described above. Minor adverse effects such as burning, stinging, irritation, folliculitis, hypertrichosis, contact dermatitis, and changes in skin pigmentation occurred in less than 10% of patients. No cases of skin atrophy were seen in two longer RCTs (of 20 weeks' and 18 weeks' duration) using histological examination and pulsed ultrasound, respectively [109,121]. No visible signs of skin atrophy were detected in RCTs of children and adults after 4 weeks of twice-daily potent topical steroid followed by intermittent application for 12–20 weeks [78,107,111,112]. In a further RCT including 376 adults, one patient developed visible signs of skin atrophy (telangiectasia) during 4 weeks of daily potent topical steroid treatment [110]. No serious systemic effects or cases of skin atrophy were reported with regular topical steroids of mild to moderate potency in a longer cohort study in 14 prepubertal children (median treatment period 6.5 years) [123]. Temporary suppression of the hypothalamic–pituitary–adrenal axis is uncommon [119]. Enhanced topical steroid absorption and temporary suppression of the hypothalamic–pituitary–adrenal axis have been demonstrated with wet-wrap dressings in patients with severe widespread eczema [118].

Four very small RCTs in healthy volunteers (12 adults) have used ultrasound to evaluate skin thickness after topical steroid application [124–127]. Significant skin thinning occurred after 1 week with twice-daily 0.05% clobetasol 17-propionate and after 3 weeks with twice-daily 0.1% triamcinolone acetate and 0.1% betamethasone 17-valerate. All preparations were used for up to 6 weeks, and skin thinning reversed within 4 weeks of stopping treatment. No significant thinning was reported with twice-daily hydrocortisone prednicarbate or once-daily mometasone furoate after 6 weeks. One systematic review of adverse effects of topical treatments for atopic eczema concluded that physiological side effects are uncommon and systemic effects are rare [128].

### Comments

The majority of trials of topical steroids for atopic eczema have been of short duration, even though atopic eczema is a chronic relapsing disease in which topical steroids may be required for months or years. Trials that have examined the potential benefit of weekly topical steroids for preventing eczema flares have suggested large benefits. Trials have used a wide variety of clinical scoring systems, making it difficult to compare results, and many trials have studied adults only. It is not possible to recommend a “best” topical steroid, as most trials have only compared one against another, but seldom against the same one and never all together. In the only trial comparing short bursts of potent steroid versus a longer duration of mild topical steroids, the majority of patients were recruited from primary care and had mild eczema only. Further trials involving patients with more severe disease are needed in order to define the most effective method of using topical steroids in the long-term management of the disease and prevention of relapse. It is also unclear how long an initial stabilization period needs to be in order to enjoy better subsequent long-term control. The majority of RCTs have not specifically addressed skin atrophy and have been of too short a duration to adequately assess risk with long-term use of topical steroids. The clinical significance of skin thinning, as detected by statistically significant changes in total skin thickness when measured by ultrasound, is unclear, especially as the whole point of treating thickened lichenified eczematous skin is to restore it to its normal thickness and appearance. Only one RCT has addressed the

risks of skin atrophy in children objectively using ultrasound [121], and further trials using a range of topical steroids of different strengths are needed in order to guide safe prescribing.

### Implications for practice

Although topical steroids have been used for the treatment of atopic eczema for over 40 years, surprisingly little work has been done to understand how best to use them for the long-term control of atopic eczema. Most RCTs have compared “me-too” products in studies lasting only a few weeks, instead of addressing important questions such as the optimum duration of application and whether one should use short bursts of potent steroids followed by milder preparations, or vice versa. The short-term studies have failed to evaluate the speed of onset of one type of steroid in comparison with another – an important consideration when trying to control the symptoms quickly in the child depicted in the case scenario. Despite widespread concern about skin thinning with topical steroids, which has arisen from occasional horror stories of people using very potent preparations continuously at sensitive sites such as the face or groin area for inappropriate periods, RCT evidence does not suggest that clinically significant skin thinning is a problem.

In relation to the child portrayed in the case scenario, a possible evidence-based treatment approach could involve the use of a potent topical steroid (for example, an inexpensive preparation such as betamethasone valerate once daily) for 2–4 weeks to gain remission, followed by emollient-only “steroid holidays” to allow any skin thinning to recover. Future flares could then be treated with 3-day bursts of the same potent preparation. If this should fail to achieve sufficient overall control in terms of frequency and duration of remission, another approach would be to use the same preparation every weekend on active and previously healed sites.

### Key points: topical steroids

- Older RCTs of topical steroids versus placebo suggest a large treatment effect in atopic eczema.
- It is not possible to make recommendations about the “best” topical steroid, as no RCT has compared all the available preparations of similar potency.
- There is no clear RCT evidence to support the use of twice-daily over once-daily topical steroid administration.
- There is good RCT evidence that application of twice-weekly potent topical steroid to stabilized eczema can reduce the number of flare-ups in adults and children, although further RCTs are needed to confirm the long-term safety profile of this approach in infants.
- There is no RCT evidence that skin thinning is a problem with correct use of topical steroids, although most RCTs have been of short duration and other non-RCT evidence should be considered before firm conclusions are drawn.

### Do oral antihistamines help?

Only oral antihistamine agents are considered here. For the purposes of answering the question, we have included studies whose outcome measures were global indices such as quality of life (which may actually be enhanced in the context of a sedative drug used nocturnally, but is normally decreased in conventional studies, where daytime sedation is a side effect). We also considered trials in which specific indices such as disease severity scores or itch assessments were assessed irrespective of the systemic side-effect profile.



### Efficacy

One systematic review was identified, 21 RCTs, and two subsequent RCTs. The studies are summarized in Web Table 24.3 [129–152]. Tabulation and systematic analysis of these trials revealed no clear or powerful effect of administering antihistamines to children or adults. Seven of the trials used physician-assessed global severity and five used patient-assessed global severity. The most commonly reported outcome was patient-assessed itch. The largest and longest clinical trial to date (conducted over 18 months) found no significant difference in atopic eczema severity, as measured using SCORAD, when cetirizine (a nonsedating antihistamine) was compared with placebo [150]. Another subsequent study suggests that chlorpheniramine (a sedating antihistamine) may help reduce the duration and amount of moderate to strong topical corticosteroid use [151].

### Comments

The lack of emergent clarity in these trials reflects the way many dermatology studies are powered: low patient numbers in trials intrinsically demand large treatment effects to be statistically significant. It is therefore likely, from an intuitive point of view, that no large effects will be derived from the use of antihistamines, as the everyday experience of dermatologists will already attest. The individual merits of antihistamine treatments cannot be covered by such a review; and in particular, the patient-specificity of drug effects is necessarily lost when considering aggregated cohorts and statistical means, not to mention the differences in “utility” that occur for the same drug in differing contexts. The impact of a specific context of drug administration is nowhere better seen than when comparing the sedative and nonsedative antihistamines across daytime and nighttime administrations.

### Implications for practice

Collectively, RCTs conducted to date fail to show convincing evidence of a clear benefit for oral antihistamines, regardless of whether sedative or nonsedating treatments are used. An ongoing systematic review of these trials conducted by individuals within the Cochrane Skin Group may reveal more precise conclusions if data from similar studies can be combined. In relation to the child described in the case scenario, we would not recommend the use of oral antihistamines except for very occasional use as a sedative (in which case other sedatives might be just as good).

#### Key points: oral antihistamines

- Oral antihistamines have been extensively studied.
- Over 20 RCTs on antihistamines for atopic eczema have been conducted to date, with no clear evidence of benefit, especially in the largest and longest study.
- The individuality of effect of an antihistamine on any one person or given situation is variable enough to allow us to ignore pooled studies and to go on to recommend antihistamines in those contexts, or for those patients, where a potential benefit is obvious or already noted by either the patient, physician, or carer.

### What about topical tacrolimus?

Tacrolimus is a powerful immunosuppressant drug used to prevent the rejection of organ transplants. Chemically, it is a macrolide lactone isolated from the bacterium *Streptomyces tsukubaensis*. A topical form of tacrolimus (FK-506) was developed to treat atopic eczema. Topical tacrolimus is thought to benefit atopic eczema by

inhibiting phosphatase activity of calcineurin and thereby the dephosphorylation of the nuclear factor for activated T-cell protein, which is necessary for the expression of inflammatory cytokines. Downregulation of the high-affinity IgE receptor on Langerhans cells and inhibition of release of inflammatory mediators from mast cells and basophils may also partly explain the beneficial effect of tacrolimus in atopic eczema [153,154].

### Efficacy

The systematic reviews highlighted in the last edition of this textbook [49,155] have been superseded by a flurry of nine further systematic reviews dealing with different aspects of topical tacrolimus or pimecrolimus which will be discussed in the next section. The systematic reviews may all be found on the Centre of Evidence-Based Dermatology map of systematic reviews of eczema (<http://nottingham.ac.uk/research/groups/cebd/resources/index.aspx>) and additional reviews will be added to that resource as they become available. All of the placebo-controlled trials show that topical tacrolimus (0.1% and 0.03%) works better than placebo at 12 weeks. Further trials have compared 0.03% tacrolimus versus 0.1% tacrolimus, and not surprisingly these suggest that the stronger preparation is more effective than the weaker one at 12 weeks. Such placebo-controlled studies add little to clinical decision-making. The most relevant comparators for topical tacrolimus are moderate and potent topical corticosteroids. A well-conducted systematic review in 2011 found 17 trials comparing topical corticosteroids with topical tacrolimus 0.1% or 0.03% and showed in general that tacrolimus had similar efficacy to mild to moderate corticosteroids [156]. A further six trials compared tacrolimus with potent corticosteroids. Four of these trials showed tacrolimus 0.1% to be less effective or equivalent to fluticasone (potent steroid). Another systematic review conducted in 2011, which looks virtually identical to another published the following year by the same team [157,158], looked specifically at the comparative efficacy of topical tacrolimus versus topical pimecrolimus and included four RCTs of 1834 patients with varying degrees of severity of atopic eczema and concluded that topical tacrolimus had greater efficacy than topical pimecrolimus. Specifically, they found that 0.1% tacrolimus was more effective at 6 weeks than 1% pimecrolimus in adults (relative risk [RR] of failure, 0.58; 95% CI; 0.46–0.72) and children (RR, 0.55; 95% CI, 0.34–0.88) with moderate to severe atopic eczema. They also found that fewer pediatric patients withdrew from trials due to lack of efficacy or adverse events in those using 0.03% tacrolimus compared with 1% pimecrolimus, although there was no clear difference in efficacy between the two for children with mild to moderate eczema.

Since eczema is typically a long-term condition with frequent flares, topical tacrolimus has been used in a similar way to potent topical corticosteroids for two consecutive days each week following initial stabilization in the hope of trying to reduce the frequency of future flares. The use of topical tacrolimus in such a proactive rather than reactive way was systematically reviewed by Schmitt *et al.* in 2011 [41]. They found eight trials that included 1768 patients with moderate to severe atopic eczema, three of which compared 2–3 days per week of tacrolimus ointment vehicle, and five of which compared potent topical corticosteroids (fluticasone propionate in four studies and methylprednisolone aceponate 0.1% in one study) with vehicle. Both topical tacrolimus and topical corticosteroids reduced flares by around half when compared with vehicle (for fluticasone propionate: RR, 0.46; 95% CI, 0.38–0.55; for tacrolimus ointment: RR, 0.78; 95% CI, 0.60–1.00). No head-to-head studies of topical tacrolimus versus topical corticosteroids

have been done, but the meta-analysis above suggests a slightly greater effect for topical corticosteroids, which is also probably less expensive [159].

### Drawbacks

The RCTs and various safety studies published to date suggest that topical tacrolimus is a safe drug, at least in the short term. Very little of the drug is absorbed systemically. Transient burning at the site of application is a common phenomenon, occurring in about half of adults. Skin burning with 0.1% tacrolimus is about three times commoner than with 0.03% tacrolimus or moderate-potency topical corticosteroids [156]. Local irritation increases to 80% for 0.1% tacrolimus when applied to the head and neck area [160]. Topical irritation may be diminished with simultaneous application of a topical corticosteroid [161]. Apart from case reports, which are prone to selection bias, there is no clear evidence of an increased risk of skin or internal malignancy such as lymphoma with topical tacrolimus [128,155,162,163]. There is almost complete absence of data reported on clinically significant skin thinning or adrenal gland suppression.

### Comments

There is little doubt that topical tacrolimus is an effective drug for atopic eczema in comparison with vehicle, with some gains in efficacy for the stronger 0.1% preparation. The drug appears to be safe in the short term, although it should be borne in mind that tacrolimus is a potent immunosuppressive, and more data will be needed on skin infections such as herpes simplex and eczema herpeticum. Longer term surveillance data using validated databases will also be needed on the subsequent risk of internal malignancies such as lymphoma. Given that topical tacrolimus is likely to be applied frequently to facial skin – a frequent site for atopic eczema involvement – there is a need to carefully evaluate the risk of excess skin cancer on areas of the skin exposed to the sun.

It is always helpful to have a few alternatives for treating a chronic disease like eczema. What is less clear for the practicing physician is where exactly topical tacrolimus fits in with the other currently available therapies, such as topical corticosteroids [164].

Studies summarized in the systematic review suggest that 0.1% topical tacrolimus is superior to weak topical corticosteroids, but probably less effective than potent topical corticosteroids [155]. Some have suggested that topical calcineurin inhibitors can be used with topical corticosteroids either simultaneously (at the same or different body sites) or sequentially, but the evidence base in terms of efficacy and drawbacks of such an approach is still sparse [165,166].

Topical tacrolimus has been licensed in the USA and UK for the treatment of people with moderate to severe atopic eczema that is not adequately responsive, or who are intolerant of conventional therapies. Yet – rather oddly, however – none of the RCTs has been conducted specifically in people in whom topical steroids have failed. In other words, the evidence base is completely absent for the very group of people in whom it is recommended for use. This raises the question of why product licenses were granted for such second-line use, given the lack of relevant evidence to inform such a decision. The percentage of atopic eczema sufferers who are truly “unresponsive” to topical steroids is probably very small (around 10% of patients with severe cases seen in secondary care) [167]. It is likely, therefore, that the drug will be used in a much wider group of topic eczema patients as an alternative to topical corticosteroids – a prediction that is likely to be fulfilled, given existing widespread and often unjustified public fear of using topical steroids [168].

The lack of skin thinning with prolonged use of topical tacrolimus is a distinct advantage over topical steroids when the latter have to be used in excessive quantities for sites that are prone to skin thinning, such as the face. Even so, clinically significant skin thinning with intermittent use of topical steroids is rare in modern clinical practice [169], and it is odd that none of the trials to date has demonstrated a clear reduction in clinically noticeable skin thinning with topical tacrolimus in comparison with optimum use of topical corticosteroids – given that lack of skin thinning is one of its main selling points [170]. Some case series have suggested that there is a good response of facial atopic eczema and atopic blepharitis to topical tacrolimus [171–173], and these may be two scenarios in which the drug will prove to be particularly useful.

One detailed cost-effectiveness technology appraisal using Markov modeling of chronic eczema conducted for the UK Health Technology Assessment Programme in 2005 found wide uncertainty in estimating the cost effectiveness of tacrolimus in comparison with standard treatment [174], although another cost-effectiveness study from Sweden suggested that topical tacrolimus was cost effective in comparison with standard therapy [175]. The use of topical tacrolimus to prevent eczema flares is supported by good evidence, but such a proactive effect has already been demonstrated for potent topical corticosteroids [41].

### Implications for clinical practice

Given the lack of crucial comparisons surrounding the introduction of topical tacrolimus, physicians and patients are still probably guessing as to how and when it should be used. The lack of a skin thinning effect may point to it being particularly useful when patients with moderate to severe disease are “stuck” on their topical steroid preparations and have to use such preparations almost continuously. Topical tacrolimus may be particularly useful for resistant facial atopic eczema, for similar reasons. Physicians should resist using such a preparation as a “steroid alternative” until more relevant RCT and safety data become available.

#### Key points: topical tacrolimus

- It is good to have additional effective topical treatments for people with moderate to severe atopic eczema.
- Topical tacrolimus (0.03% and 0.1%) works much better than vehicle only.
- Topical tacrolimus 0.1% and 0.03% has been shown to be superior to a very weak topical corticosteroid (1% hydrocortisone) in children with moderate to severe atopic eczema.
- Topical tacrolimus 0.1% is probably less effective than potent topical corticosteroids.
- Topical tacrolimus can be used for 2–3 days each week to prevent flares in those with initially stabilized eczema, but it is possibly not as effective as topical fluticasone when used in such a proactive way.
- Topical tacrolimus appears to be safe in the short term.
- Transient burning occurs in about half of adults, and is more common than with topical corticosteroids.
- Long-term data are needed on local and systemic infection, skin cancer rates, and internal cancers such as lymphoma.
- Paradoxically, none of the studies to date has tested topical tacrolimus for its suggested use as a second-line treatment for atopic eczema.
- In relation to the child described in the case scenario, we would use topical tacrolimus only when standard therapy with short bursts of once-daily potent topical steroids (or very mild preparations for the face), emollients, and educational support had failed.

### How might topical pimecrolimus be used?

Like tacrolimus, pimecrolimus is a macrolide immunosuppressive drug [176]. It is currently available in many countries worldwide for “short-term intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant to conventional therapies” [177]. The primary indication of use is almost identical to that described for topical tacrolimus, except that pimecrolimus is aimed at mild to moderate atopic dermatitis whereas tacrolimus is aimed at moderate to severe atopic dermatitis. Given that mild atopic eczema is about 10 times more frequent than moderate to severe disease [18], the market could be a lot larger for pimecrolimus. Pimecrolimus has also been used to prevent disease flares.

The mode of action of pimecrolimus is thought to be similar to that of tacrolimus and ciclosporin in preventing the release of calcineurin-mediated cytokine and proinflammatory mediators from mast cells and T cells [154].

### Efficacy

A Cochrane systematic review conducted in 2007 included 31 trials of 8019 participants showed that pimecrolimus was significantly more effective than vehicle (the cream base not containing pimecrolimus) in the short term [178]. That review also found nine RCTs of preventing flares in 3091 participants over a 6-month period, a finding confirmed in another systematic review [179]. The Cochrane review also found that topical pimecrolimus was significantly better than vehicle in preventing flares (at 6 months: RR, 1.47; 95% CI, 1.32–1.64) and with better quality of life in the intervention group. No direct comparisons between pimecrolimus and tacrolimus for preventing flares could be found. Pimecrolimus was less effective than topical corticosteroids, but too few studies had been done at that time to comment on a direct comparison with topical tacrolimus. A subsequent systematic review in 2011 undertook a meta-analysis of four RCTs of 1843 participants which had compared topical pimecrolimus against tacrolimus and found that 0.1% tacrolimus was more effective than 1% pimecrolimus for adults (RR, 0.58; 95% CI, 0.46–0.72) and children with severe eczema (RR, 0.55; 95% CI, 0.34–0.88) at week 6 [157]. There was no significant difference between 1% pimecrolimus and 0.03% tacrolimus in children with mild to moderate atopic eczema, but this was only based on two short-term studies, and the confidence intervals around these estimates were wide. One study has explored the value of topical pimecrolimus for children who are intolerant of or who have become dependent on topical corticosteroids for facial eczema [180]. Not surprisingly, topical pimecrolimus was shown to be better than vehicle alone. Another study of 376 children tried to evaluate whether addition of 1% pimecrolimus to fluticasone conferred additional benefit, and although the addition of pimecrolimus did not seem to increase adverse effects, no clinical benefit in eczema severity or time to clearance was noted [181].

### Drawbacks

Data from RCTs do not suggest any serious adverse effects to date [174,178]. Application reactions of burning, warmth, stinging, and soreness have been consistently reported in the RCTs and are dose related. Pimecrolimus 1% skin irritation and burning was not significantly different from vehicle in the 2005 systematic review (pooled rate from six trials, 0.87; 95% CI, 0.70–1.09), but skin

burning was higher with pimecrolimus than with topical corticosteroids [174]. The systematic review did not show any increase in skin infections with pimecrolimus 1%. Adverse events such as burning and itching were about the same in the two systematic reviews conducted in 2010 and 2011 [157,179]. Skin thinning does not seem to occur with topical pimecrolimus, whereas mild topical corticosteroids can result in transient skin thinning on the face, the clinical relevance of which is unclear [170]. Systemic absorption does occur with pimecrolimus, but this is very small in the majority of people [182,183]. No skin atrophy has been observed in a detailed study comparing topical pimecrolimus with 0.1% betamethasone valerate cream when applied to the forearms of healthy volunteers continuously for 4 weeks [184]. However, this type of study is difficult to interpret, as potent topical steroids are not used in this way and the effects of disease on skin thickness cannot be assessed.

As pimecrolimus is an immunosuppressive agent, the theoretical long-term risk of cancer needs to be monitored [163,185], given that the drug is likely to be prescribed in large quantities to millions of children with mild forms of this common disease.

### Comments

The quality of reporting in the pimecrolimus studies was generally good. There is no doubt from the many vehicle-controlled studies that pimecrolimus is effective in treating atopic eczema in terms of reducing symptoms, improving physical signs of eczema, and improving the quality of life. Yet despite the profusion of vehicle-controlled studies (which some might consider unethical, given that several early studies established efficacy) [186], numerous open-label studies, and consensus statements produced by physicians with conflicts of interest, the key comparisons between pimecrolimus and current commonly used treatments for mild to moderate conditions – that is, mild to moderate topical corticosteroids – appear to be completely missing. The early study that compared pimecrolimus with betamethasone showed that betamethasone was much more effective, and adding pimecrolimus to topical corticosteroids did not confer any gains. Some studies suggest that topical pimecrolimus might be useful in people who are intolerant of topical corticosteroids or who become dependent on them. Terms such as “intolerance” or “dependency,” although reasonably defined in some study protocols [180], have a wide possible interpretation and could include many who are simply anxious about using topical corticosteroids. Some atopic eczema patients do become “addicted” to inappropriate use of topical corticosteroids [187], especially on the face, and these patients might well benefit from topical pimecrolimus or tacrolimus. The studies that evaluated the use of pimecrolimus applied at the first sign of a flare to reduce the flare severity and frequency appear interesting (and at least they address the chronic relapsing nature of atopic eczema [49]) – until, that is, one realizes that they are effectively placebo-controlled studies. It could have been the case that early treatment with very mild and safe 1% hydrocortisone acetate ointment would have averted the development of flares equally well. Others have pointed out that it is normal to wait until a flare becomes moderate to severe before initiating treatment with a topical corticosteroid, and in that sense the prevention-of-flare studies are somewhat unrealistic [188]. As a result of missing studies, the physician and patient are left guessing about how pimecrolimus compares with the best standard therapy [189].

One detailed economic assessment concluded that there was too much uncertainty in assessing the cost effectiveness of pimecrolimus [174], although a later study suggested that pimecrolimus



was cost effective in comparison with standard therapy in a US setting [190]. Previous technology appraisals on pimecrolimus and tacrolimus by the UK National Institute of Health and Clinical Excellence have resulted in both being included as second-line treatments for atopic eczema in children [52].

### Implications for practice

In relation to the child described in the case scenario, the lack of key comparisons in published trials makes it difficult to decide with the child's parents when and how to use topical pimecrolimus. We would consider pimecrolimus if the child needed to use potent topical steroids almost continuously in order to obtain a reasonable quality of life, although we would not be too optimistic about the ability of pimecrolimus to work where potent topical corticosteroids had failed. We might use topical pimecrolimus for persistent sensitive-site eczema (such as on the face) if topical corticosteroids or topical 0.03% tacrolimus had failed or caused too much burning or stinging. We would also consider trying pimecrolimus if the child's parents were letting the child suffer terribly from uncontrolled eczema because of an irrational fear of using any form of topical steroids, although we would probably use tacrolimus 0.1% first. We would also consider trying topical pimecrolimus to prevent flares in children with brittle disease if prevention of flares with topical corticosteroids or topical tacrolimus was ineffective.

### Key points: topical pimecrolimus

- Pimecrolimus 1% cream works better than vehicle cream in children and adults with mild to moderate atopic eczema. There is no need for any more vehicle-controlled studies of pimecrolimus.
- Like topical tacrolimus, pimecrolimus 1% could be useful for eczema in sensitive sites such as the face if topical corticosteroid use is no longer effective or use is excessive.
- Topical pimecrolimus is probably less effective than tacrolimus.
- Topical 1% pimecrolimus cream is much less effective than topical betamethasone valerate in atopic eczema.
- Pimecrolimus 1% has not been compared with 1% hydrocortisone or other mild to moderate topical corticosteroids for short-term or long-term treatment for reasons that are unclear.
- Some evidence supports the notion that pimecrolimus is better than vehicle in people who have adverse effects from topical corticosteroids.
- Topical 1% pimecrolimus does not cause skin thinning.
- Local application-site reactions such as burning are common, mild, and transient.
- Topical pimecrolimus appears to be safe in the short term, although its long-term safety is unknown.
- It is not known whether early treatment with topical pimecrolimus is any better than early treatment with a weak topical steroid such as 1% hydrocortisone or 0.03% topical tacrolimus in preventing disease flares.
- Independent studies are needed in order to compare the cost effectiveness of pimecrolimus with standard bursts of mild to moderate topical steroids in the short-term control of mild atopic eczema in children, and to see whether early use of either treatment approach improves disease control over a longer period.

### Will interventions to reduce house dust mite improve this child's eczema?

#### Efficacy

This section deals with house dust mite eradication for cases of established atopic eczema. No systematic review was found

for house dust mite reduction in atopic eczema. However, a recent Cochrane systematic review of house dust mite reduction for the treatment of asthma reported no improvement in the symptoms of asthma [191]. The authors concluded that "It is doubtful whether further studies, similar to the ones in our meta-analysis, are worthwhile."

Seven RCTs [192–198] evaluating the role of house dust mite reduction in the treatment of *established* atopic eczema were identified and are summarized in Web Table 24.4. Trials were excluded if they looked at the prevention of atopic eczema in newborn children (for example, Koopman *et al.* [199] and Horak *et al.* [200]), because the results were not presented for atopic eczema in a disaggregated form (for example, Terreehorst *et al.* [201]), or because data were not presented on the clinical impact of the interventions (for example, Nishioka *et al.* [202]). In general, the evidence to support the efficacy of house dust mite eradication for the treatment of atopic eczema is of poor quality. Interventions such as vacuuming and the use of synthetic mattress covers appear to be most effective in reducing the house dust mite load, but how this impacts on disease severity is still unclear.

The first small RCT by Colloff *et al.* [192] evaluated the daily use of natamycin (a spray used to kill house dust mites) versus a matched placebo spray with and without vacuum cleaning in a parallel-group study for 4 months in 20 young adults with atopic eczema. The authors demonstrated that it was the vacuum cleaning and not the natamycin spray that had a significant impact on reducing house dust mite numbers. There was no significant clinical improvement in those who had been allocated to natamycin versus placebo. The mean symptom score (maximum score 288) in the natamycin and vacuum group changed from 55.2 at baseline to 38.6 at 4 months, in comparison with 45.2 to 35.8 in the group with no natamycin and no daily vacuuming.

A second small, but important, RCT was conducted by Tan *et al.* in 1996 [193], with duplicated publication in 1998 and again in 1999. Tan *et al.* randomly assigned 60 patients (30 adults and 30 children) for a total of 6 months to an intensive dust mite eradication regimen involving Gore-Tex (Intervent, UK) bedding covers, benzyl tannate spray to kill mites and denature their allergens, and a high-filtration vacuum cleaner, or to a control group with plain cotton bedcovers, placebo spray, and a standard upright vacuum cleaner with poor filtration performance. One trained nurse applied the bedcovers and spray each week, and participants were encouraged to vacuum their bedrooms daily. There was a dramatic and very similar reduction in the concentration of house dust mite major allergen (*Der p1*) in bedroom carpets in both the active and placebo treatment groups at the end of 6 months. Disease activity – as recorded in terms of surface area involvement and with a composite severity score (maximum score 108) measured at one point at the end of the 6 months – was reduced by a small amount in both groups, but more so in the active group. The mean reduction in scores for the active and placebo groups were 12.6 and 4.2 units, respectively. Those in the active treatment group had more severe conditions to begin with, and so an analysis of covariance was conducted to allow for baseline scores and initial house dust mite antigen levels. This showed a mean difference of 4.2 in the change of score (95% CI, 1.7–6.7 units;  $P = 0.008$ ) between the two treatments. Further analysis also suggested that it was changes in the mattress and carpet dust in the bedroom that mediated much of the treatment effect. Subgroup analysis suggested that only children had a clinically and statistically significant benefit, and that there was no correlation between

clinical improvement and positive skin prick tests at the study outset.

Another small study in Japan by Endo *et al.* [194] evaluated the potential benefit of intensive vacuum cleaning in the rooms of 30 children with atopic eczema for a total of 12 months. Both groups were visited every 3 weeks by a team of mite specialists, who either cleaned room floors, mattresses, and quilts very thoroughly and encouraged parents to clean in the same way in between visits, or performed a less intensive clean (vacuum suction power reduced to 50%) with similar cleaning between visits. Parents were thus unblinded to the intervention. A statistically significant decrease in mite numbers in favor of the intensive cleaning group was only noted for the room floors. Clinical scores, as evaluated by a physician blind to treatment allocation, were significantly improved in the active group in comparison with baseline, but not in the control group. Clinical scores were given in graphic form only, and the appropriate statistical test of mean difference between the two treatments was not reported.

Oosting *et al.* [195] compared Gore-Tex mattress, duvet, and pillow covers with placebo covers made from cotton for a period of 12 months. Eighty-six children and adults took part, all of whom had atopic eczema and were allergic to house dust mite. Whilst the mattress covers resulted in a significant reduction in the house dust mite load, no significant between-group differences were observed in clinical features or self-reported itch and sleep loss.

The remaining studies were all very small (41 participants [196], 20 participants [197], and 43 participants [198]), making conclusions difficult.

### Drawbacks

None of the studies reported any adverse events of the house dust mite removal treatments. This does not necessarily imply that none occurred. The imposition of daily vacuuming for a long period has a cost in terms of time for parents and sufferers, as does the purchase of a high-filtration vacuum cleaner, impermeable mattress covers, and mite sprays.

### Comments

Given the strong circumstantial evidence to suggest that house dust mite allergens may play a part in atopic eczema, it is a pity that so few studies on house dust mite avoidance have been performed. Those that have been done tend to be small, and it is difficult to generalize in the absence of more pragmatic studies. The method of randomization and concealment was not reported adequately in any of the studies, and no intention-to-treat (ITT) analyses were performed (although drop-out rates were quite low).

Further studies that separate the different interventions for reducing house dust mite are needed. It is important that such trials should be as pragmatic as possible to determine which groups respond best, which interventions are the most cost effective, and whether the laborious interventions are sustainable in less-motivated people.

### Implications for clinical practice

In the absence of strong clinical trial data to support the use of house dust mite avoidance measures, the decision as to whether the cost and effort of implementing such procedures is warranted probably lies with the individual families. In the future, specific immunotherapy with a house dust mite preparation may be possible, and early tests have shown promising results [203].

### Key points: house dust mite

- Seven randomized controlled trials have been reported, although methodological difficulties and small sample sizes limit the interpretation of the results.
- Future, large-scale pragmatic trials are needed if this issue is to be resolved.
- In the meantime, the use of allergen-impermeable mattress and pillow covers, coupled with regular vacuuming of the room, appear to be the best way of reducing house dust mite if such changes are truly beneficial.

### Will an exclusion diet (such as a milk- or egg-free diet) alone help reduce the symptoms of this child's atopic eczema?

This section deals with exclusion diets for cases of established atopic eczema. Four systematic reviews were found. Only one Cochrane review later published in *Allergy*, with a search ending in 2006, looked exclusively at exclusion diets in established atopic eczema [204,205]. This review included nine RCTs, and since then no RCTs looking at exclusion diets have been published. Two [206,207] of the remaining three reviews used the Cochrane review as their primary evidence source [205]. The nine RCTs examining the role of elimination diets in established atopic eczema are summarized in Web Table 24.5.

### Efficacy

No evidence of benefit from elimination diets was found in the trials that included unselected participants with eczema; however, there was some evidence from one trial [208] of an egg-free diet in infants with a proven specific IgE to egg of a beneficial effect. Two trials [209,210] did not find any evidence that elemental diets were beneficial for eczema compared with a standard hospital diet in adults or a pre-existing formula in children. A study of a few-foods diet [211] with whey and a few-foods diet with casein hydrolysate or a normal diet found no beneficial effects from either of the few-food diets.

### Drawbacks

Calcium, protein, and calorie deficiency are risks associated with the use of dairy-free diets in children. Such diets should only be used under medical supervision. Three RCTs used soya-based milk substitute, which itself can be allergenic in atopic eczema.

### Comments

Methodological difficulties mean that interpretation of these trials is difficult. RCTs that employ a parallel design with an unblinded normal control diet may introduce bias in favor of the active group. In addition, those trials that place all participants on exclusion diets and then reintroduce the suspected offending food, in comparison with a control, risk introducing another allergen (for example, soya) or introducing the suspected allergen (for example, cows' milk) in a way that does not mimic real life. Poor concealment of randomization allocation, lack of blinding, and high drop-out rates without an ITT analysis all mean that the above studies should be interpreted with great caution. Future studies should ideally be longer term and more pragmatic and should ensure that randomization is concealed.



Uncontrolled elimination diets followed by double-blind, placebo-controlled challenges with foods suspected to aggravate symptoms have also been tried in atopic eczema [212–216]. These studies are not the same as RCTs of food elimination. Instead, they try to answer the question: “Does food X make a particular child’s atopic eczema worse?” The precise relationship between such food challenge studies and long-term benefits of exclusion of the suspected foods to atopic eczema sufferers is not clear. Blood and skin-prick tests are usually only helpful in predicting clinical response if they are negative [217,218]. It should also be borne in mind that a high negative predictive value has only been shown in relation to the provocation of symptoms after a double-blind challenge, and not the clinical response following food elimination, which is not necessarily the same thing. The relationship between atopic eczema and food sensitivity is a complex one, and readers are referred to a clear evidence-based work by David for further information [219].

### Implications for clinical practice

Elimination diets are difficult for families and patients to follow, even in the highly motivated environment of a clinical trial. In the absence of clear evidence of the involvement of a particular food substance, the possible harms may outweigh the benefits. In cases in which exclusion diets are indicated, appropriate dietary advice and support should be made available.

#### Key points: exclusion diet

- There is little evidence to support a diet free of eggs and milk in unselected patients with atopic eczema.
- There is no evidence to support the use of an elemental or few-foods diet in atopic eczema.
- There is some evidence to support the use of an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs.
- The most common diets used are those free of milk or eggs.
- The possible risks of impaired growth and development in children should be recognized.

### Do probiotics, prebiotics, or synbiotics help reduce the symptoms of this child’s atopic eczema?

It has been suggested that probiotics (commonly referred to as “good” bacteria that have the ability to modify immune responses) and prebiotics (substances which have been shown to assist the growth of “good” bacteria) or a combination of these (“synbiotics”) might help prevent and treat atopic eczema by way of altering the intestinal microflora [220].

This section deals with probiotics used to help reduce the symptoms of atopic eczema. Three systematic reviews [221–224] were found, all published in 2008, with the most up to date being a Cochrane review, also published in *Clinical and Experimental Allergy*, with a search ending April 2008. The Cochrane review and the two other reviews all included the same 12 RCTs [220,225–235]. One review also included an additional RCT looking at the effects of probiotics on levels of polyunsaturated fatty acids, but no clinical outcomes. Including the trials published since the Cochrane review, a total of 27 RCTs have so far evaluated the role of probiotics, prebiotics, and synbiotics in the treatment of *established* atopic eczema [220,225–250]. These are summarized in Web Table 24.6.

Seven of the 27 studies use extensively hydrolyzed formula milk to avoid cows’ milk [220,225,226,228,230,232,237].

### Efficacy

All three systematic reviews [221–224] found *no convincing evidence* that probiotics confer clinically meaningful benefit for treating established eczema. The seven trials published since then have mostly provided *evidence of no benefit* for single-strain probiotics, particularly *Lactobacillus rhamnosus*, for treating established eczema [237,240–242,244,248,249].

There is *evidence of no benefit* from three trials for mixtures of probiotic strains compared with placebo, whether or not the participants had a cows’ milk allergy or sensitization to one or more allergens [227,235,238]. These trials all found significant benefits for post hoc subgroups with raised IgE levels. The trials of lactobacilli strains of probiotics mostly do not show any significant benefits compared with placebo or in addition to standard treatments. These mostly small trials were in quite selective populations and gave little detail about which outcomes and statistical outcomes were prespecified.

Four trials compared different synbiotic combinations against inactive placebo or a placebo of hydrolyzed formula given to both groups [236,239,243,245]. Three of these trials found a significant benefit for eczema severity from synbiotics after 8 or 12 weeks [236,239,243], with one of these positive results only being found in a possibly post-hoc subgroup of IgE-associated eczema [239]. One trial [234] compared a synbiotic mixture with a prebiotic preparation alone and found no significant difference in SCORAD at the end of the study. Two trials [247,250] of prebiotics compared with placebo or no treatment were difficult to interpret, as clinically relevant between-group analyses were not reported.

The seven studies looking at elimination diets together with probiotics and synbiotics showed no significant differences in eczema severity between the treatment groups and placebo.

### Drawbacks

Around half of the trials reported information about adverse events, and although the levels of adverse events were often quite high, only a few were thought to be related to treatment. Recruitment in one study [226] was prematurely terminated due to concern over adverse gastrointestinal symptoms, which were limited to the group receiving heat-inactivated *L. rhamnosus* GG.

### Comments

The only positive results have mostly been from post hoc sub-analyses of IgE-associated “atopic” eczema, but no trial has yet prospectively assessed such a group, and so the results must be treated with caution. Most of the trials were small with little or no detail about the method of randomization, allocation concealment, blinding, and which outcomes were prespecified. Most of the trials did not analyze the results using an ITT principle, and withdrawals were often relatively high. Short-term outcomes, selective populations, and a lack of clear reporting of results all mean that probiotics may have potential for individuals from populations not studied and for longer time periods. One abstract of a trial on *Lactobacillus reuteri* seems to indicate a significant reduction in extent of eczema, sleep loss, and itching from once-a-day supplementation per day for a year [246]. There was not enough detail in the abstract to assess this trial properly. The full trial report is awaited with interest.

**Key points: probiotics, probiotics and synbiotics**

- There is little convincing evidence that probiotics produce a clinically useful effect for the treatment of atopic eczema.
- There is some evidence to suggest that a subset of patients who test positive for IgE might benefit from the use of probiotics.
- Trials are needed in these specific subsets of eczema patients before probiotic treatment can be recommended.
- Synbiotics show some weak evidence of benefit, but this is not strong enough to recommend the use of these probiotic and probiotic mixtures in clinical practice.
- There is not yet any evidence that prebiotics alone are beneficial for eczema compared with placebo or no treatment.

**Do Chinese herbal medicines improve the symptoms of atopic eczema?****Efficacy**

Chinese herbal medicines are commonly used in Asian clinical practice and are usually taken as a decoction by boiling them in water, and drinking the “tea” produced, or as external applications directly to the skin. The mode of action points towards anti-inflammatory and immunosuppressive properties by downregulating local T-cell-mediated reactions.

Seven systematic reviews have included assessment of Chinese herbal medicines for eczema [49,251–256] and 10 RCTs have been published [257–266].

**Zemaphyte** Five trials evaluated a commercial preparation of 10 traditional Chinese herbs, comprising *Ledebouriella seseloides*, *Potentilla chinensis*, *Clematis armandii*, *Rehmannia glutinosa*, *Paenia laciflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza glabra*, and *Schizonepeta tenuifolia* (Zemaphyte). This preparation is no longer available.

One double-blind RCT compared Zemaphyte in a decoction and a placebo comprising of a mixture of “inert” plant materials, used once daily for 8 weeks in 47 children with atopic eczema [257]. Median percentage changes in the clinical scores for erythema in comparison with baseline were 51% for Chinese herbs and 6.1% for placebo. Change in surface damage was 63.1% and 6.2% in the Chinese herb and placebo groups, respectively. A 1-year follow-up study of the children concluded that Chinese herbal medicine, in the medium term, was helpful for approximately half the children who originally took part in the RCT [267].

A similar double-blind RCT, involving 40 adult patients with atopic dermatitis, used the same intervention and similar trial methods [258]. Significant improvements were reported for blinded assessments of erythema ( $P < 0.001$ ) and surface damage ( $P < 0.001$ ) with the herbs in comparison with the placebo.

A third double-blind crossover RCT evaluated Zemaphyte in comparison with “inert plant” placebo [260]. Forty participants with atopic eczema were randomized to Zemaphyte or placebo for 8 weeks, followed by a 4-week washout period before using the alternative therapy for a further 8 weeks. This trial found no significant differences between the groups, except for lichenification at week 4.

In addition, two RCTs have evaluated Zemaphyte used as an infusion, compared with a more palatable form of freeze-dried granules [259,261]. These trials included 18 and 32 adults with moderate to severe atopic eczema, respectively [259,261]. Both

trials followed up patients for a period of 8 weeks and found no significant differences between the groups.

**PentaHerbs** This product is a five-herb concoction containing *flos loniceriae*, *herba menthae*, *cortex moutan*, *Rhizoma atractylodis*, and *cortex phellodendri*. One trial compared PentaHerbs given in capsules for 12 weeks against placebo [263]. Eighty five children and young adults from 5 to 21 years with moderate to severe eczema (SCORAD over 15) took three capsules twice a day. There were no significant differences between the groups in the severity of eczema assessed using the SCORAD scale, but quality of life (measured using CDLQI) showed a significant improvement for the PentaHerb group compared with placebo at the end of treatment ( $P = 0.008$ ) and at 4 weeks post therapy ( $P = 0.059$ ). There was also a trend towards reduced topical steroid use in the PentaHerb group compared with placebo.

**Siberian ginseng, Achillea millefolium and Lamium album** One double-blind RCT compared a herbal preparation of Siberian ginseng, *Achillea millefolium* and *Lamium album* against placebo. Both products were taken orally three times a day for 2 weeks, with follow-up for 1 year [262]. The trial included 49 participants with moderate atopic eczema. Participants were allowed to continue with established emollients and topical corticosteroid therapy. All participants experienced a fall of around 15 to 20 points in eczema severity after 2 weeks of treatment, but there was no significant difference between the groups. Daytime pruritus and sleep loss also showed no significant difference between the herbal preparation and placebo.

**Jiawei Danggui Decection** An open trial of 47 children and adults aged 12 years and over assessed the addition of Jiawei Danggui Decection to standard care of a non-sedating antihistamine (loratadine 10 mg per day) plus a potent topical corticosteroid (hydrocortisone butyrate 0.1% once a day for 4 weeks) [264]. All participants had a diagnosis of atopic eczema. The active treatment group received 250 mL Jiawei Danggui Decection in addition to standard care, but the treatment regimen was not reported. In the active treatment group, 56% (14/25) of participants showed an improvement in eczema severity (using the six-area, six-sign atopic dermatitis (SASSAD) scale) of greater than 70%, compared with 22.7% (5/22) in the standard care control group ( $P < 0.05$ ).

**Xiao-Feng-San** This product is a mixture of 13 different plant materials commonly used for the treatment of eczema in Asian clinical practice. In a double-blind RCT including 71 children with refractory atopic eczema, Xiao-Feng-San was compared with a placebo of caramel, lactose, and starch that tasted similar to the active treatment [266]. Participants were randomized at a ratio of 2:1 in favor of the active treatment group and took the treatment three times a day for 8 weeks, followed by a no-intervention follow-up phase of a further 4 weeks (12 weeks in total). Participants had eczema on more than 20% of their body surface area and had no active infection or exudation. Only 56 of the 71 participants completed the trial, but analysis was conducted on an ITT basis to account for this. The primary outcome of eczema severity using a blinded lesion score decreased significantly in the active treatment group compared with placebo at 8 weeks (reduction of 79.1 points  $\pm 5.7\%$  vs 13.5 points  $\pm 7.6\%$ ;  $P < 0.001$ ). Similar statistically significant results were also found for erythema, surface damage, pruritus, and sleep

loss at 8 weeks. All but erythema remained significant 4 weeks after the end of treatment at the 12-week assessment.

**Hochu-ekki-to** This is a traditional herbal medicine containing 10 species of medicinal plants. The product is thought to benefit patients with a delicate, easily fatigable or hypersensitive constitution known as *Kikiyu*. A multicenter, double-blind RCT included 91 patients aged 20–40 years with atopic eczema and a Kikyu constitution (as defined using a scoring questionnaire) [265]. Participants were randomized to Hochu-ekki-to taken twice daily for 24 weeks, or an inactive placebo of similar appearance, smell, and taste. All participants continued with their standard eczema treatments throughout the trial. Eighty-four participants were included in the analysis set, and of these 77 completed the 24-week treatment period. No between-group differences were observed in the mean skin severity scores at 24 weeks, although comparison of those whose skin severity score had reduced to zero at 24 weeks favored the active treatment group (19% vs 5%;  $P = 0.06$ ). Percentage change from baseline in the amount of topical medication used (following adjustment for potency of the medication) also showed a statistically significant difference in favor of the active treatment group ( $P = 0.05$ ), suggesting that Hochu-ekki-to may be a useful steroid-sparing treatment in this population, without increasing the severity of the eczema.

### Drawbacks

Many of the trials reported that the herbal remedies were unpalatable, resulting in attempts to produce alternative formulations, such as freeze-dried preparations [259,261]. The most commonly reported adverse events were nausea and diarrhea, stomach discomfort, loose bowels or flatulence, dizziness and headache, or increased visits to a general practitioner.

The potential for hepatotoxicity is a concern with Chinese herbs. However, the six studies that carried out pretreatment and post-treatment blood tests found no significant changes in blood chemistry or renal function [257,258,260,261,265,266]. One participant had a transient elevation of aspartate aminotransferase which returned to normal levels within 8 weeks after the treatment was stopped.

### Comments

All studies were randomized, but the method and concealment of allocation were rarely described and ITT analysis was only conducted in one trial [266]. It is also questionable whether the placebo plants were truly inert. Clearly, larger scale RCTs of longer duration, using comparable methods and interventions, are needed.

### Implications for clinical practice

Ten RCTs have now been conducted looking at a variety of herbal preparations, and have demonstrated mixed treatment response. Of the eight RCTs to have compared active treatments against placebo, six reported significant beneficial effects; although the two trials by Sheehan and Atherton [257,258] were not supported by a subsequent trial of the same product [260]. The most promising remedies would appear to be Xiao-Feng-San, which was found to be beneficial in the highest quality of the reported trials [266], *PentaHerbs* [263], *Jiawei Danggui Decection* [264], and Hochu-ekki-to [265].

Further research is needed to address the long-term safety implications.

### Key points: Chinese herbal medicines

- Ten randomized controlled trials of modest size are reported, including a variety of interventions.
- Lack of standardization and replication of trial results using the same herbs makes it difficult to interpret these findings.
- Further large-scale studies are needed to clarify the role of Chinese herbal remedies in the treatment of eczema.
- A number of side effects were identified, the true implications of which cannot be addressed without long-term studies.

### What are the most appropriate washing and bathing routines for patients with atopic eczema?

#### Efficacy

**Frequency of bathing** Eczema patients are often advised to take regular baths to hydrate the skin [52], but there is a lack of clarity over the best ways of doing this, and patients often ask for recommendations on the frequency and duration of bathing [268]. We found no RCT evidence on the frequency of bathing, the use of baths compared with showers, or on the most appropriate temperature of the water.

**Soaps and soap substitutes** The use of soap is discouraged in patients with eczema, with an emphasis of “complete emollient therapy” that includes the use of soap substitutes [52,53]. However, there is little guidance on what soap substitutes are most effective and how they should be used.

We found one RCT [269] that examined the use of a liquid soap (Axera) containing 12% ammonium lactate and 20% urea, compared with commercially available liquid soap of similar odor and cleaning properties. This 3-week trial included 36 children and adults with mild to moderate eczema, who were randomized 2:1 in favor of the active intervention. Participants continued with their usual eczema treatments, with the exception of other soap or emollients. Blinding of outcome assessment was unclear. After 3 weeks, significant improvements were reported compared with the control soap group in investigator-rated scaling ( $P < 0.0001$ ), skin dryness ( $P < 0.0001$ ) and redness ( $P = 0.03$ ), and in patient-reported itch ( $P < 0.0001$ ). However, it is not clear why participants were asked to refrain from using normal emollient therapy during the trial, and it is possible that these results reflect a lack of emollient therapy in the control group.

**Antiseptic wash products** The role of antiseptic soaps and antiseptic bath products has been discussed in the section on infected eczema.

**Bath additives** Bath emollients are often recommended on the grounds that they are an easy way of applying emollients to the skin; particularly for young children who may not cooperate in allowing the application of topical medications. Bath emollients have also been advocated as a way of avoiding the use of bubble bath in children with eczema, and clinical guidelines recommend their use [52,53]. One systematic review has looked specifically at the use of bath emollients in the treatment of eczema [270] and found no RCT evidence to support their use. The use of antimicrobial bath products and bleach baths are included in the section on infected eczema.



**Washing of clothes** Detergent enzymes may cause skin irritation, leading some physicians to advise patients with atopic eczema to avoid the use of such detergents in favor of alternative “nonbiological” detergents [271]. We located one RCT testing the hypothesis that enzyme-containing detergents are more likely to aggravate atopic eczema than a nonbiological detergent [272], and one that looked at the impact of using fabric softeners in adults with atopic dermatitis [273].

In the first study [271], 26 adults with mild to moderate atopic eczema (mean age 25 years) were randomly assigned in a double-blind crossover study to use either a trial detergent containing enzymes or a visually identical detergent without enzymes for 1 month. There was a 1-month wash-out period before randomization, when participants used their usual washing powder. Topical steroids were permitted during the study and were weighed. In the 25 patients who completed the trial, there was no difference between the two groups in terms of disease severity (SCORAD scores of 29 in each group; 95% CI for mean difference, 4–5). Similar results were found for the use of topical steroids, patient-reported itch, and eczema activity.

The study looking at fabric softeners [273] was a single-blind randomized trial using a left–right comparison design for a period of 12 days. Twenty volunteers with a history of atopic dermatitis were enrolled in the study (none had active lesions at the time of enrolment). In order to simulate realistic conditions of skin damage, sodium lauryl sulfate was applied to each volar forearm under occlusion 3 days before the start of the study. A control patch using water was also applied to each arm. Repetitive wash tests were performed three times a day using softened or unsoftened fabric in random order to each arm. The investigator was blinded to the fabric used at each site. Both for the control and pre-irritated skin, all measured parameters indicated that “softened” fabric was less aggressive to the skin than “unsoftened” fabric.

**Water hardness** There is epidemiological evidence suggesting a possible link between water hardness and eczema prevalence [274,275]. One large RCT [276] involving 336 children with atopic eczema randomized participants to receive an ion-exchange water softener plus normal care, compared with normal care alone for a period of 12 weeks. The trial was assessor-blind since it was not possible to blind trial participants to their treatment allocation. Emphasis was placed on objective outcome measures such as eczema severity (using the SASSAD eczema severity scale), nighttime movement/scratching (measured using accelerometers) and topical medication use. No between-group differences were reported for any of the objective outcome measures, and the primary outcome of eczema severity showed no differences between the groups, with narrow confidence intervals (mean difference, 0.66 points; 95% CI, –1.37 to 2.69;  $P = 0.53$ ). Statistically significant differences were seen between the active and the control group in subjective outcome measures, including self-reported symptoms, quality of life, and well-controlled weeks. However, these results are likely to be subject to considerable expectation bias, and the magnitude of effect was small, suggesting that these differences were of little clinical relevance.

### Drawbacks

**Frequency and duration of bathing** Water is becoming an increasingly scarce and valuable resource, making it harder to justify the use of baths over showers without evidence of clinical benefit.

**Bath emollients** These products are extremely expensive compared with standard leave-on emollients.

**Washing of clothes** No patients had contact dermatitis to enzymes when patch-tested at the end of the study, and there was no evidence of specific blood IgE against any of the enzymes [273].

**Water softeners** These products represent a large capital expense for eczema patients.

### Comment

Although the study by Andersen *et al.* [272] was small, the virtual absence of any differences between the enzyme and nonenzyme detergents and the corresponding narrow confidence intervals provide convincing evidence of a lack of harmful effect. The study was not sponsored by industry.

The independently funded trial of ion-exchange water softeners also provides strong evidence for lack of effect of this intervention in the management of established eczema [276]. This was a large trial, with a low risk of bias and narrow confidence intervals around the objective primary outcome of eczema severity, making it unlikely that a clinically important effect had been missed.

### Implications for clinical practice

There is good evidence that water softeners do not provide additional benefit over normal care in the management of eczema. There is currently no evidence to suggest that parents should switch from a biological to a nonbiological washing powder. Further long-term studies using a pragmatic design are required to establish the role of bath emollients, frequency of bathing, and the most appropriate wash products to use.

### Key points: washing and bathing

- There is strong RCT evidence that softening hard water for washing and bathing does not improve the severity of established eczema.
- Although the parents of children with atopic eczema commonly avoid washing powders that contain enzymes (biological powders), evidence from a small RCT did not support the belief that washing detergents containing enzymes have a provoking effect on eczema severity in comparison with washing detergents without enzymes.
- There is limited evidence to suggest that fabric softeners may be less likely to exacerbate the symptoms of eczema; further pragmatic studies are needed.
- The role of soap substitutes and bath additives in the management of eczema requires further study.

### Can specialist clothing help reduce the symptoms of atopic eczema?

#### Efficacy

Wearing fabrics next to the skin has been suggested to be a physical irritant that can be a trigger for eczema. A small RCT showed that smooth fibers are less aggravating for eczema patients than rough fibers [277], and fabrics manufactured using warp-knit appear to be less irritating than jersey-knit fabrics, regardless of the fibers used [278]. Cotton, silk, and smooth manmade fibers have all been



used to create specialist clothing for people with eczema. These garments sometimes have added antimicrobial properties.

Three systematic reviews have evaluated the use of therapeutic clothing that has antimicrobial properties [279–281]; but no recent reviews were identified looking at all clothing or fabric-types.

The most recent systematic review [279] included a section on antimicrobial clothing and reported two RCTs of silk clothing [282,283] and two on silver-impregnated clothing [284,285]. Two further RCTs have examined the use of ethylene vinyl alcohol (EVOH) fiber [286,287], which does not have antimicrobial properties.

**Silk clothing** One trial included 22 children with mild to moderate eczema. It compared sericin-free silk tubular bandages (DermaSilk®) on one arm for 3 months against 2 weeks of sericin-free silk fabric without the antimicrobial properties of DermaSilk on the opposite arm, followed by cotton bandages for the remaining 10 weeks [282]. The second trial included 30 children and adults with atopic eczema. It compared sericin-free silk sleeves (Dermasilk) against the same fabric without the impregnated antimicrobial, used for 28 days [283].

Both trials hinted at the possible benefit of Dermasilk fabric using blinded outcome assessment of eczema severity, but they were too small and of too short a duration to inform clinical practice. No trials were identified for other brands of silk clothing.

**Silver-impregnated clothing** One trial included 68 adults with moderate eczema, and compared silver-coated undergarments (Padycare®) with cotton undergarments. Both were worn day and night for 2 weeks [284]. A second trial included 30 children and adults with “acute eczema.” Participants received one of three interventions for 2 weeks: silver-coated undergarments (x-static®); undergarments without the silver-coated fibers; or prednicarbate ointment 0.25% [285]. All participants could use prednicarbate ointment 0.025% as required throughout the trial.

Neither trial presented convincing evidence of efficacy. Interpretation of the trial findings is difficult owing to the small sample sizes, lack of blinding, and short-term duration of the trials.

**Ethylene vinyl alcohol fiber** EVOH is a smooth fiber that is reported to be highly hydrophilic with good biocompatibility. This product has been used for tissue engineering, vascular grafts, tissue repair, wound healing, and drug delivery.

An 8-week crossover RCT included 30 participants with well-maintained eczema and compared EVOH underwear (MEDIELE®) with cotton underwear. Each participant wore each type of underwear for 4 weeks without a wash-out period in-between the different fabrics [286]. A second RCT included 24 children aged 3–9 years with eczema and compared EVOH underwear with cotton underwear for a period of 4 weeks [287].

No significant differences in eczema outcomes were found between the groups in either of these small trials.

### Drawbacks

The main drawbacks for specialist clothing are its cost and limited availability.

None of the trials reported adverse events related to the use of specialist garments other than [285], in which one patient was reported to have 1 µg of silver per liter in their urine at day 28. No silver deposits were found on the skin or mucous membranes.

### Comment

The study of specialist clothing is challenging because of the inability to blind participants effectively, making it difficult to interpret the significance of patient-report outcomes. This is particularly problematic as the possible benefits of these garments may be at a sub-clinical level, impacting on overall comfort and improvements in sleep and quality of life. No studies have yet been conducted looking at the cost effectiveness of specialist clothing.

### Implications for clinical practice

There is no need for parents of children to buy expensive cotton clothes if their child finds that other fine-weave synthetics are just as comfortable.

On the basis of the limited trial data to date, it is not yet possible to establish whether specialist clothing provides measurable benefits for patients with eczema. Nevertheless, these garments are currently available on prescription and their popularity amongst patients is growing. A large, well-designed, pragmatic trial is needed to see whether such clothing offers a genuine benefit to patients with eczema.

### Key points: specialist clothing

- The roughness of clothing textiles may be more important for skin irritation than the type of textile fiber (synthetic or natural).
- Several types of specialist clothing are now available for the treatment of eczema, but the quality of the trials to date makes it difficult to assess their clinical benefit.
- Of the products currently tested in RCTs, silk garments are the only ones to have demonstrated significant improvements in eczema severity using blinded outcome assessments.
- A large, well-designed pragmatic trial is needed to see whether such clothing offers genuine benefits for patients with eczema.

### What is the role of psychological interventions for the treatment of atopic eczema?

#### Efficacy

Over the years, a range of psychological interventions have been used for the treatment of eczema, including behavioral management (often referred to as habit-reversal techniques), relaxation therapy, and cognitive behavioral therapy.

Two systematic reviews have looked at psychological interventions for eczema [288,289]. The first included psychological and educational interventions in children only, and the latter included all psychological intervention trials. The role of education in the management of eczema is discussed in the education section of this chapter. This section describes four RCTs of psychological interventions: two habit-reversal trials [290,291]; one relaxation with hypnotherapy and biofeedback trial [292]; and one trial including both relaxation and cognitive behavioral techniques [293]. A fifth trial included relaxation and habit reversal as part of an educational package, and this is described in the section on the role of education in the management of eczema [294], and one trial of brief dynamic psychotherapy was excluded as it was not randomized [295].

**Habit reversal** It has been postulated that scratching becomes a habit in atopic eczema, and that it is detrimental in patients with eczema because it further damages the skin. Habit reversal is a modified behavioral technique that teaches patients to recognize

the habit and then to progressively develop a “competing response practice,” such as simply touching, squeezing, or tapping the itching area, or to develop other ways of moving their hands away from the itching area [296].

In the first habit-reversal study [290] 17 patients with eczema aged 19–41 years were randomly assigned to two groups. The interventions consisted of hydrocortisone cream plus two sessions of habit-reversal treatment, received during week 1 (active-treatment group), or hydrocortisone cream alone (comparator group). The study was unblinded. At the end of the assessment period (28 days), the mean reduction in the global eczema score was 67% in the active-treatment group, in comparison with 37% in the comparator group ( $P < 0.05$ ). The total score for self-assessed annoyance was also markedly reduced in the active group in comparison with the other group. The mean percentage reduction of scratching episodes per day was 79% in the active-treatment group, in comparison with 49% in the comparator group ( $P < 0.01$ ).

In the later study conducted by the same team [291], 45 patients were randomly assigned to four groups for a period of 5 weeks. Group A applied hydrocortisone cream for the entire 5-week period; Group B applied betamethasone valerate (a potent topical steroid) for 3 weeks, followed by hydrocortisone for the remaining 2 weeks; group C applied hydrocortisone plus habit-reversal for the 5-week period; and group D had betamethasone plus habit-reversal for the first 3 weeks, followed by hydrocortisone plus habit-reversal for the remaining 2 weeks. The study was unblinded. Significant differences were reported between the behavioral-therapy groups and those taking steroids alone for “total skin status.” Scratching was reduced by 65% in the hydrocortisone-only group, 74% in the betamethasone followed by hydrocortisone group, 88% in the hydrocortisone plus habit-reversal group, and 90% in the betamethasone plus hydrocortisone plus habit-reversal group (statistics not presented).

**Relaxation with hypnotherapy and biofeedback** One 20-week trial included 44 children who had inadequately controlled eczema, despite conventional treatment [292]. Participants were allocated to three treatment groups: relaxation plus hypnotherapy; relaxation plus biofeedback; and a discussion group control in which children were encouraged to keep a treatment diary. All sessions lasted approximately 30 min, with four sessions in total at 2, 4, 6, and 8 weeks. The hypnotherapy sessions focused on reducing itching through guided imagery with a clinical psychologist, the biofeedback sessions used a “relaxometer” that gave feedback to participants about their level of relaxation using skin conductance, and the discussion control group discussed their symptoms on the basis of their diary responses.

Children in the hypnotherapy and biofeedback groups both showed a statistically significant reduction in the blinded outcome assessments of severity of surface damage and lichenification compared with the control group. For the combined relaxation groups there was a significant improvement after 20 weeks compared with baseline for surface damage ( $t = 2.2$ ;  $P = 0.04$ ) and lichenification ( $t = 2.39$ ;  $P = 0.027$ ). There was no improvement over time in the discussion (control) group. Drop outs were high for this trial, with 12/44 (27%) being excluded from the analysis at 20 weeks.

**Relaxation and cognitive behavioral therapy** One study evaluated the use of an autogenic training program (ATP) as a form of relaxation therapy versus cognitive-behavioral therapy (BT), versus a standard dermatological educational (DE) program versus com-

bined DE and BT (DEBT) [293]. A total of 113 secondary-care patients were randomly assigned to these four groups and were also compared with an additional standard medical treatment group, who were not part of the random assignment. The investigators were blinded to the group allocation. The intervention was for 3 months, and the patients were followed up for 1 year. At the end of 1 year, the mean skin severity lesion score dropped from 29.5 to 28.8 in the DE group, from 33.7 to 19.8 in the ATP group, from 31.0 to 20.7 in the BT group, and from 35.4 to 25.8 in the DEBT group. There were no significant differences in the mean severity of itching between the four groups. The DEBT treatment led to significantly greater improvement in global skin severity than intensive education (DE) alone, and this was also accompanied by significant reductions in topical steroid use. Overall, the drop-out rate was low (9/113; 8% at 3 months).

### Drawbacks

In the study by Ehlers *et al.* [293] the behavioral approaches required 12 weekly group sessions of 1.5–2 h, each with five to seven patients. No adverse events were reported in any of the trials, although some of the drop outs could possibly be related to the fact that extra visits were needed for the behavioral technique.

### Comments

The study by Ehlers *et al.* [293] and the study by Sokel *et al.* [292] carry more weight than the other two studies [290,291] as the assessments were made by an investigator blinded to the treatment allocation.

Despite methodological limitations, the magnitude of improvement for those receiving behavioral techniques in addition to standard dermatological care (which included topical corticosteroids) warrants further investigation.

### Implications for clinical practice

The combination of psychological therapy with judicious use of topical corticosteroids and emollients seems an attractive one, and evidence from four RCTs suggests that this approach may be successful. The exact components of the most effective psychological therapy package are still to be established, and the lack of suitably qualified personnel may limit the ability to deliver this intervention in many settings.

### Key points: psychological interventions

- Four RCTs suggested that psychological interventions such as habit-reversal, cognitive behavioral therapy, relaxation, hypnotherapy, and biofeedback are a useful adjunct to dermatological treatment in atopic eczema.
- Further studies are required to assess how these findings can be generalized to other settings and patient groups.

### What is the role of patient education in controlling the symptoms of atopic eczema?

#### Efficacy

This section deals with patient education as delivered to patients and their families. It does not explicitly deal with studies examining the impact of changes to service delivery. Three systematic reviews

were found [289,297,298] and one additional RCT [299] not included in any of the reviews. A total of 11 RCTs are described below [294,299–308]; two studies [309,310] were excluded, as there were participants with eczema and psoriasis (and did not present data in a disaggregated form).

Whilst the content of the training programs varied, information was generally covered relating to the nature of the disease, treatment options (including practical advice and treatment expectations), coping strategies/psychosocial support, and avoidance of allergens and irritants.

### *Efficacy*

**Adults with eczema** One 40-week study [294] of 54 adults aged 18–35 years in the Netherlands compared a 2-week (10 days) intensive day-school program made up of two 3-h sessions per day in groups of five participants with communal breaks against standard outpatient care. A significant improvement in quality of life between the treatments groups was reported, resulting in a median difference of 13 points after 40 weeks. The time taken for consultations showed a greater reduction after 40 weeks in the education program. A lower level of sick leave at 10 weeks in the education group which did not reach significance was not apparent at the end of trial.

One trial [299] randomized 80 adults with eczema to either a paper pamphlet or an online video containing the same eczema education information which could be used as often as desired for 12 weeks. There was a significantly greater satisfaction and level of knowledge with the online video compared with the pamphlet. The severity of eczema was also significantly reduced after 12 weeks in the online video group in comparison with the paper pamphlet group.

**Children with eczema, parents and carers** Three trials compared a single additional education session on top of usual care [302,303,307]. A trial [302] involving 61 children with eczema and their parents compared a 2-h group education session in addition to normal care. A significant decrease in eczema severity in the education group was reported at 4 weeks and 12 weeks. Quality of life improvement was only significant for children aged 5–16 years at 12 weeks, but not for children under 5 years. There was no significant on-family impact. A large primary care trial in the UK [303] compared a newly qualified dermatology nurse giving one 30-min consultation, compared with no consultation in 225 children with eczema. The control group was offered the same consultation after the end of the study. This “one-off” nurse education session did not appear to have any effect on the children’s quality of life after 12 weeks. The impact on the family improved after 4 weeks compared with having no consultation ( $P = 0.06$ ; mean difference,  $-0.79$ ; 95% CI,  $-1.62$  to  $+0.04$ ), but this effect was not present at 12 weeks. It is not clear whether there was any effect on the severity of eczema as no data other than baseline were provided. An open trial [307] evaluated the use of an “eczema school” for parents of 50 consecutive children seen in an outpatient setting (aged 4 months to 6 years). The families received either routine information from the treating physician, or a two hour visit with a trained dermatology nurse in addition to the physician visit. There was generally a trend towards improved outcomes for the group that had received the additional education sessions, but the results were poorly reported and are difficult to interpret. Improvements in disease severity were judged to be largely a result of better treatment compliance.

Three trials compared a program of additional education on top of usual care. A trial [304] of 151 children with eczema in the USA

used an individual, tailored session with a trained eczema educator for 15 min for the initial visit, with the level of follow-up being dependent on the severity of eczema. The control group was given standard care by a resident and attending pediatric dermatologist. It is not clear when the outcomes were measured, but no significant difference in severity was reported between the treatments. Two almost identical trials were reported by Staab and colleagues [300,301]. The first trial [301] compared a parental multidisciplinary education program, with 93 participants receiving one 2-h session a week for 6 weeks and 111 participants not receiving any sessions. A much larger study [300] by the same authors in Germany in 2006 looked at the use of a standardized group education program in 518 infants and children from 3 months to 7 years, 185 children aged 8–12 years with their parents, and 120 adolescents aged 13–18 years. The training programs for the two trials were almost identical and both trials followed the participants for 1 year. The parental education program in the first trial showed no significant reduction in severity after 12 weeks; however, the education programs for the three different age groups in the second trial reported significant reductions in eczema severity in the education group in comparison with the control group. The adolescents (13–18 years) had the most significant improvement, with a reduction of  $-14.5$  points ( $P < 0.0001$ ). The older children (8–12 years) had a reduction in severity of  $-8.2$  (95% CI,  $-13.6$  to  $-2.8$ ;  $P = 0.003$ ). The infants and young children (3 months to 7 years) had a reduction in severity of  $-5.2$  (95% CI,  $-8.2$  to  $-2.2$ ;  $P = 0.0002$ ). Both studies by Staab and colleagues found significant reductions in quality-of-life scores. In the smaller 2002 trial [301], the “confidence in medical treatment” subscale was the only one to show a notable benefit from one session of education. In the much larger trial in 2006 [300], the 3 months to 7 years age group showed a significant benefit of education for all five subscales. The 8–12 years age group showed a benefit of education for the confidence in medical treatment, emotional coping, and acceptance of disease subscales. For all the significant differences in quality of life, the absolute difference in points reduction was small: between 1 and 3 for all scales. An assessment of how itching behavior was affected by education in 8–18-year-olds found that catastrophication (thoughts of not being able to cope) significantly improved, but that coping did not improve. Education was found to be the biggest predictor of change in treatment behavior using logistic regression.

One small study from Brazil [306] in 36 families with a child of 2–16 years with moderate to severe eczema compared attending fortnightly 90-min support group sessions for 6 months with a control group. It was not clear whether the control group had any intervention or not during the study. For the support group intervention, the children and adults were taken into separate sessions and joined together for a short time at the end. The frequency of pruritus decreased in the support group compared with baseline, but it is unclear whether this was significantly better than the control group. The influence of itching on the participant’s mood was statistically significantly reduced in the support group compared with the control group after the intervention, but this was a relatively small absolute difference. The children’s quality of life (CDLQI) was reported as statistically significantly different as a whole, after the intervention ( $P = 0.01$ ). The leisure ( $P = 0.04$ ) and personal relationships ( $P = 0.02$ ) were reported as statistically significantly improved in their own right for the support group compared with the control group. No data were given for these reported statistical differences.



A small trial in Germany [308] randomly assigned 30 children aged 3–6 years with moderate to severe atopic eczema to either a 10 min demonstration with a Kardoff–Schnelle–Parker skin model or a control group verbal instructions of the same duration as a standard consultation. The skin model is made of chamois leather and allows the children to experience for themselves the difference between well-moisturized and neglected skin. The sessions took place at baseline and again at 14 days. The main outcome of eczema severity was assessed blindly at 0, 14, and 42 days. Children allocated to the active group showed significant improvements in their SCORAD scores at 42 days ( $P < 0.006$ ).

Another trial [305] allocated patients to one of three groups: parental education ( $n = 18$ ); standardized video education for parents plus a handbook ( $n = 15$ ); or standard eczema therapy and follow-up ( $n = 14$ ). There were significant differences between the groups at baseline in terms of disease severity and maternal education that were not adjusted for in the analyses. Significant improvements were seen for the education groups in comparison with the control group in relation to disease severity, sleep, itch, and quality of life, although multiple hypothesis testing meant that the implications of these findings were difficult to assess.

### Drawbacks

There was no information reported on adverse events or other disadvantages from any of the trials of educational interventions.

### Comments

Around half of the trials clearly described an appropriate method of randomization and allocation concealment. Blinding of the outcome assessors, which in most trials was both the investigators and the participants, was either not clearly described, not attempted, or not possible owing to the differences in treatment between the groups. Several of the trials had high numbers of participants who did not complete the trial and were not included in the analyses.

### Implications for practice

For adults, an intensive education course shows some evidence of benefit, but this would probably have meant 2 weeks off work, which on its own could lead to an improvement in a chronic condition such as eczema. The format of the education should be taken into account for adults as it appears to have a significant impact. Offering choice of format may be a good way to maximize the benefit for individuals.

The education programs for parents, young children, and adolescents appear, on average, to confer some benefit, mostly by reducing severity or increasing disease-related quality of life, or both. The effects appear to be complex and may be related to age, presence or absence of parents or children, and format of the education and the providers of the education. There is not yet enough evidence to recommend a particular format or content for educational interventions. It is worth noting that adolescents (13–17 years) that were educated mostly without their parents showed the greatest decrease in eczema severity, although the large numbers of drop outs were not included in the analyses for this trial. This age group is also more likely than younger children to improve spontaneously, so this must be treated with some caution. The most interesting result from the only trial to have looked at the role of support groups is that the quality of life and effect of itching on mood of the children with eczema significantly improved whilst impact on the whole family did not. This trial [306], along with evidence from other trials, hints at the potential benefit of child-

focused, semi-structured support groups for children with eczema, although which particular aspect or aspects of the group support may be conferring this benefit needs much more detailed investigation.

The wider applicability of the educational interventions trialed is difficult to interpret, as an educational intervention developed in one country or in a particular population may not have the same effect in another. None of these trials has yet reported potential harms of educational interventions or the cost effectiveness of these interventions and their suitability for use in routine practice, points which must be considered when managing patients and their families using education.

### Key points: patient education

- Seven randomized controlled trials have been reported that broadly support the role of education in the treatment of atopic eczema (although some lacked power to show an effect).
- Most trials included children or adults with moderate or severe disease.
- The evidence to support the use of multidisciplinary education packages in group therapy sessions is better than that for individualized therapy.
- There is evidence to support “child-focused” education, particularly for older children and adolescents with eczema.
- Trials of individual therapy based on a single consultation with a health professional were less conclusive and require further investigation.
- Positive results have been observed up to 1 year following delivery of the education intervention.

### Case scenario 24.2: How should infected atopic eczema be treated?

Bacterial, viral, and fungal infections may be associated with atopic eczema (Figure 24.2). Infections need to be promptly recognized and treated. Confusion arises because atopic eczema skin may be colonized with pathogens in the absence of signs of clinical infection. The role of these pathogens in aggravating eczema is unclear, and the distinction between what constitutes clinically infected and noninfected eczema requires further clarification.

The relationship between *S. aureus* and atopic eczema disease activity has been debated for many years. Most physicians recognize clinically infected eczema as recent onset of weeping, oozing, and serous crusting or overt pus overlying the eczematous lesions. In this situation, *S. aureus* is isolated in 90–100% of cases, usually in high numbers [311,312]. Recent reports show increasing emergence of methicillin-resistant *S. aureus* in eczema sufferers [313–316]. In around 30% of cases,  $\beta$ -hemolytic streptococci are also isolated [311]. Recurrent clinical infections are a major problem for some atopic eczema sufferers [317].

*S. aureus* is also isolated from the lesions of atopic eczema in 50–90% of patients without overt signs of infection [318,319]. Some studies have shown that *S. aureus* may promote inflammation through superantigen activation [320].

The significance of the yeast *Malassezia furfur* in atopic eczema is also a subject of debate. It exists in two forms: *Pityrosporum ovale* and *Pityrosporum orbiculare*. There is some evidence that it can act as an allergen, stimulating both positive radioallergosorbent tests (RASTs), and positive patch tests, which may exacerbate eczema [321,322]. It has been particularly implicated in atopic eczema of the head and neck [323].





Figure 24.2 Infected atopic eczema.

The idea that bacteria and fungi may act as immunogenic stimuli contributing to atopic eczema activity has led to a large increase in the use of anti-infective agents in nonclinically infected atopic eczema over the last 20 years. This section evaluates the possible benefit of these agents.

A Cochrane systematic review “Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema” [281] and its subsequent update [324] are the source of much of the data in this section. We searched the GREAT database for further RCTs up to end 2011 (<http://www.greatdatabase.org.uk/>).

A total of 10 RCTs evaluating the possible benefit of oral or topical antimicrobials in clinically infected atopic eczema were included and are summarized in Web Table 24.7. An additional eight RCTs evaluating the possible benefit of antiseptics in noninfected atopic eczema are presented in Web Table 24.8. Further RCTs of topical steroid–antibiotic combinations in noninfected eczema are shown in Web Table 24.9.

### How useful are systemic antibiotics?

#### Efficacy

**Clinically infected eczema** Two RCTs evaluating systemic antibiotics for clinically infected eczema were located (Web Table 24.6) [312,325].

A study of oral cefadroxil showed significant benefit over placebo for all clinical and microbiological outcomes [312].

Erythromycin acetate and erythromycin stearate both improved clinical and microbiological outcomes. There was no significant difference between the preparations [325].

**Clinically uninfected or unspecified eczema** Two further important RCTs have compared systemic antibiotics with placebo in the treatment of noninfected atopic eczema. In the first [326], oral flucloxa-

cillin 250 mg four times daily for 4 weeks showed no benefit over placebo in terms of clinical efficacy, despite significantly reducing *S. aureus* counts. The second study [327] showed a similar absence of benefit for 2 weeks’ oral cefuroxime. Rapid recolonization occurred in both groups after cessation of treatment.

#### Possible drawbacks

Gastrointestinal side effects occurred in 50% of patients in each group taking erythromycin, one patient on cefuroxime, and 6.5% of patients on cephalexin. Emergence of methicillin-resistant *S. aureus*, which persisted for 2 weeks after completion of treatment, was noted in the flucloxacillin study.

#### Comments

The existing studies are old, and quality of reporting was generally poor, with small numbers of patients and a lack of detail regarding concurrent treatments and clinical outcomes.

#### Clinical implications

It is common practice to prescribe a short course of oral antibiotics in acute infected eczema. There is some evidence that this improves clinical signs of infection, and there is no evidence of a detrimental effect. In contrast, there is no evidence to support the use of longer term antibiotics in people with atopic eczema whose skin is colonized with *S. aureus*, and there is some evidence that use of such antibiotics may promote antibiotic resistance.

### Do topical antibiotics have a role in infected eczema?

#### Efficacy

**Clinically infected eczema** One RCT has evaluated topical antibiotics in the treatment of clinically infected eczema (Web Table 24.6).

Gentamicin was significantly less effective at reducing dermatitis activity than betamethasone valerate–gentamicin or betamethasone valerate alone [328].

**Clinically uninfected or unspecified eczema** Two RCTs have looked at topical antibiotics in noninfected eczema. One crossover study comparing 2% mupirocin ointment versus placebo in adults and children found a significant reduction in *S. aureus* in the mupirocin group compared with the placebo in the first period. However, recolonization occurred during the 4-week follow-up period [329]. A further study showed that fusidic acid 2% cream resulted in more treatment failures than hydrocortisone–fusidic acid [330].

#### Possible drawbacks

Minor skin irritation or eczema flare occurred in 18% of patients in the fusidic acid group, in comparison with only 3% in the steroid–fusidic acid group [330].

#### Comments

Topical antibiotics appear to be effective at reducing *S. aureus*, but clinical benefit of antibiotic alone is limited. Rapid recolonization occurs after cessation of treatment. Studies did not look for emergence of resistant organisms.

#### Clinical implications

The role of short-term topical antibiotics in infected atopic eczema is unclear. They may be a useful addition to topical steroids, but there is a lack of information regarding comparison between oral and topical antibiotics in this situation. Long-term use in

noninfected eczema should be avoided owing to risk of antibiotic resistance.

### Are topical steroid–antibiotic combinations more effective than topical steroids alone in clinically infected atopic eczema?

#### Efficacy

**Clinically infected eczema** We found six studies evaluating topical steroid–antibiotic combinations for clinically infected eczema (Web Table 24.6). Several other studies have not been included because they include less than five patients, or results for atopic eczema could not be separated from other dermatoses.

Two studies compared topical steroid–antibiotic combinations versus placebo. The study by Thaci *et al.* [331] showed superior benefit of betamethasone–fusidic acid ointment and cream over vehicle alone. A similar study showed superior benefit of both betamethasone/fusidic acid lipid cream and betamethasone–fusidic acid standard cream formulation compared with lipid cream vehicle alone [332].

Three RCTs have compared topical steroid–antibiotic combinations versus topical steroid alone. There was no significant difference in clinical signs or symptoms between betamethasone valerate–fusidic acid [333] versus betamethasone valerate, or between betamethasone valerate–gentamicin versus betamethasone valerate [328].

Most recently, Gong *et al.* compared mupirocin plus hydrocortisone butyrate versus vehicle plus hydrocortisone butyrate in a mixed group including 119 patients with atopic dermatitis, infected and noninfected. There was no difference in the global severity scores (EASI) or isolation rates of *S. aureus* between the groups at days 7, 14, or 28 [334].

One RCT has compared different steroid–antibiotic combinations. There was no significant difference between 0.1% betamethasone–2% fusidic acid and 0.1% betamethasone–0.5% neomycin in terms of clinical efficacy or ability to eradicate *S. aureus* [335].

**Clinically uninfected or unspecified eczema** Six further RCTs were located that have evaluated topical steroid–antibiotic combinations in nonclinically infected atopic eczema (Web Table 24.8).

Five of the RCTs compared topical steroid–antibiotic combinations versus topical steroid alone. One study of 30 participants with severe atopic eczema found clobetasol propionate 0.05% cream was as effective as betamethasone valerate 0.1% cream plus neomycin at reducing *S. aureus*, and significantly better at improving global outcome [336].

One study of 36 participants found that fluocinolone acetonide plus 0.5% neomycin sulfate cream significantly reduced the amount of *S. aureus* isolated compared with fluocinolone acetonide cream alone [318].

A further study found that 2% fusidic acid plus 1% hydrocortisone was significantly better than 1% hydrocortisone alone at reducing *S. aureus*, but there was no benefit in reducing atopic eczema activity [330].

Schuttelaar and Coenraads compared 3% tetracycline plus 0.1% triamcinolone versus 0.1% triamcinolone in 44 adults with moderate/severe atopic eczema and found no significant difference in SCORAD at the end of treatment. Significantly fewer people on the combined group had *S. aureus* isolated at the end of the study [337].

The most recent study of 60 children and adults with moderate to severe eczema found no significant difference in clinical scores (SCORAD) at 8 weeks between fluticasone propionate 0.05% cream versus tacrolimus 0.03% ointment, versus fluticasone plus 2% fusidic acid versus tacrolimus plus 2% fusidic acid. All groups reported a decrease in colonization rate of *S. aureus* after 2 and 8 weeks of treatment. Tacrolimus alone was slower to reduce *S. aureus* than fluticasone alone (significant difference at 2 weeks) with no significant benefit from the addition of fusidic acid [316].

Pooled analysis in the Cochrane review of two studies [318,337] showed an 83% reduction in the isolation rate of *S. aureus* in the combination groups compared with steroid alone at the end of treatment.

One RCT compared different steroid–antibiotic combinations. There was no difference in clinical improvement or *S. aureus* reduction between 2% fusidic acid–0.1% betamethasone cream versus 2% mupirocin ointment plus 0.1% betamethasone cream [338].

#### Possible drawbacks

Minor skin irritation, flare of dermatitis, and possible hypersensitivity reactions occurred in 1–3% of patients across the groups. Pooled results from two studies [330,337] in the Cochrane review found no significant difference in adverse events requiring withdrawal from treatment; however, there were significantly fewer minor adverse events not requiring withdrawal from treatment in the combination groups [281]. One study reported emergence of fusidic-resistant strains of *S. aureus* in two patients after 8 weeks of fusidic acid treatment [316].

#### Comments

There is evidence that topical steroid–antibiotic combinations are effective in the treatment of clinically infected atopic eczema, but there is a lack of evidence to determine how they compare with oral antibiotics combined with topical steroids or with topical steroids alone.

There is no evidence to suggest benefit for the use of topical steroid–antibiotic combinations over topical steroids alone in noninfected eczema. Topical steroid–antibiotic combinations appear to be more effective at reducing *S. aureus* than topical steroids alone, but this does not translate to clinical benefit. Rapid recolonization occurs on cessation of treatment, and hypersensitivity and bacterial resistance may develop.

#### Clinical implications

There is no good evidence for the use of topical steroid–antibiotic combinations. If they are used, they should be limited to short-term (<2 weeks) use for clinically infected eczema as per National Institute for Health and Clinical Excellence guidelines, UK [52]. There is no evidence to support long-term use in noninfected eczema and there is potential for harm.

### How effective are antifungals?

#### Efficacy

**Clinically infected eczema** There are no RCTs of antifungal treatments in infected eczema.

**Clinically uninfected or unspecified eczema** We identified six RCTs evaluating antifungal treatment for noninfected atopic eczema.

Three RCTs compared oral antifungals with placebo. In the first study, 80 patients with atopic eczema and positive skin prick or

RASTs to yeasts were randomized to ketoconazole 200 mg daily for 30 days or placebo. The ketoconazole group showed significant improvement compared with baseline at 30 days, not seen in the placebo group. Benefit was most marked in the group with positive skin cultures for *P. ovale* [339].

One study showed no difference in clinical benefit between 3 months' ketoconazole and placebo despite reduction in specific IgE to *M. furfur* and other yeasts [340].

One study compared itraconazole 200 mg daily or 400 mg for 7 days with placebo. There was significant reduction in SCORAD at day 7 in the itraconazole groups compared with placebo, but no significant difference in patient or investigator global outcome in any of the groups [341].

A further three RCTs were located which looked at the role of topical antifungals. One study [342] attempted to evaluate antifungals in atopic eczema of the head and neck area. Miconazole-hydrocortisone cream plus ketoconazole shampoo was compared with hydrocortisone cream plus placebo shampoo. There was a significant benefit in favor of miconazole-ketoconazole for reduction in *P. ovale*, but there were no significant differences between the groups with regard to clinical outcome. One study [343] compared 1% ciprofloxolamine cream twice daily for 28 days with base cream for head and neck eczema. No other treatments were allowed. The investigator's global assessment showed significantly better improvement in the ciprofloxolamine group over the study period, but the difference in EASI scores was not significant. The third study showed no benefit of hydrocortisone 1%-miconazole cream over hydrocortisone 1% alone in 30 children with atopic eczema of elbows and knee flexures [344].

### Possible drawbacks

No adverse effects were documented in most of the studies. Two patients on long-term (3 months) ketoconazole reported nausea and abdominal pain. With topical antifungals, minor skin irritation and possible hypersensitivity reactions were seen in up to 5% of patients across the groups.

### Comments

It is difficult to draw conclusions about the role of antifungals from these small and disparate studies. More work is needed to determine the relevance of positive cultures, skin prick tests, and patch tests to yeasts in patients with eczema of the head and neck.

### Clinical implications

There is no current evidence to support the routine use of antifungals in the treatment of atopic eczema.

### How useful are antiseptic agents in clinically infected atopic eczema?

This section includes topical antiseptics, antiseptic emollients, bath additives, and other antiseptic treatments. Impregnated fabrics and clothing with antimicrobial properties have been discussed in the section on specialist clothing.

Ten RCTs were located which evaluated the use of antiseptic agents in atopic eczema (Web Tables 24.6 and 24.7).

### Efficacy

**Clinically infected eczema** Two RCTs considered antiseptics in clinically infected eczema. Thirty-one children with moderate/severe eczema pretreated with 2 weeks of oral cephalixin were

randomized to bath water with added bleach plus nasal mupirocin versus normal bath water and nasal vehicle ointment. The study reported a greater mean reduction in EASI in the bleach-mupirocin group at 1 month and at 3 months compared with placebo on the body and extremities, but not on the head and neck (which the bleach did not treat) [315].

Another study of prednicarbate 0.25% cream plus dodecyl dimethyl-ammonium chloride 0.25% versus prednicarbate 0.25% cream in adults found no significant difference in global outcome at the end of treatment. Isolation of *S. aureus* was similar between groups [345].

**Clinically uninfected or unspecified eczema** Eight RCTs considered antiseptics in nonclinically infected eczema (Web Table 24.7).

**Topical antiseptics** One study of 15 children and adults with mild to moderate eczema reported a statistically significant improvement in *S. aureus* colony counts and appearance of skin lesions with povidine-iodine vs. no treatment. However, no numbers were provided and group analysis was not performed [85].

One study in 21 adults compared hyperforin 1.5% (St John's wort) cream versus placebo in a half side comparison study, and showed significantly greater reduction in SCORAD on the treatment side. No data were given on the number of patients in each group [346]. A further study (no numbers given) compared 0.2% farnesol plus 5% xylitol cream versus placebo and reported a significant improvement in dryness and scaling in both groups. At the end of treatment there was no difference between the groups in change of *S. aureus* from baseline [347].

The most recent study by Tan *et al.* compared triclosan 1% leave-on emollient cream versus vehicle cream in 60 patients all using concurrent 0.25% betamethasone valerate. At day 14 there was a significant greater decrease in SCORAD from baseline in the triclosan group compared with placebo, but by day 27 the difference was not significant. The mean total amount of steroid cream used was significantly less in the triclosan group (22 g vs 44.2 g), suggesting some possible steroid-sparing effect [71].

**Antiseptic bath additives and wash products** Two RCTs have compared a standard bath emollient, Oilatum (acetylated wool alcohols 5%, liquid paraffin 63.4%), with an emollient plus antiseptic, Oilatum Plus (benzalkonium chloride 6%, triclosan 2%, light liquid paraffin 52.5%). No significant differences were demonstrated in terms of clinical or microbiological outcomes [348,349].

A further study compared a soap containing 1.5% triclocarban with an identical placebo soap. The authors state that the global change in atopic eczema severity was significantly greater in the treatment than in the placebo group, but the actual data are missing. Graphic data suggest a similar degree of improvement in both groups [350].

One RCT compared a proprietary brand of chlorhexidine with a 1:20 000 dilution of potassium permanganate, in addition to topical steroid in both groups, and found no significant differences in the clinical or bacteriological outcomes [351].

### Drawbacks

Skin irritation, pruritus, and worsening of dermatitis were the main side effects reported in the studies in which adverse events were documented. These were reported more frequently overall in the antiseptic-treated groups.



### Comments

There is no clear evidence of additional benefit for the use of antiseptic agents in atopic eczema. The use of bleach baths appears to have some benefit, but the numbers of patients colonized with *S. aureus* was unchanged from start to the end of the study; therefore, it is not possible to attribute this benefit to reduced bacterial colonization.

### Clinical implications

Antiseptic-containing preparations are in common use in the management of atopic eczema. There is no evidence to support their routine use. It is accepted clinical practice to use antiseptics in patients with recurrent clinical infection. More studies are needed to determine whether this is beneficial, and which antiseptic agents are most effective.

#### Key points: anti-infective agents

- Twenty four RCTs of anti-infective agents are reported, the majority in nonclinically infected eczema.
- Clinically infected eczema needs to be promptly identified and treated, but there is a lack of evidence regarding best treatment.
- One small study shows a possible benefit of bleach baths and nasal mupirocin after oral antibiotic treatment of infected eczema.
- Anti-staphylococcal agents are effective at reducing *S. aureus* to a greater extent than controls, but there is a lack of evidence of clinical benefit over nonantimicrobial agents in noninfected eczema.
- The few, small studies of antifungal agents in atopic eczema do not show clear evidence of benefit.
- Adverse events reported with antimicrobial agents are low, but there remains a risk of emergence of resistant organisms after prolonged treatment.

### Case scenario 24.3: an adult with severe atopic eczema

Figure 24.3 shows a case of severe atopic eczema.

#### What is the role of systemic immunosuppressive therapy?

The systematic review by Hoare *et al.* published in 2000 described several older and experimental immunomodulatory therapies for atopic eczema, including platelet activating factor, immunoglobulins, interferon gamma, and levamisole [49]. Some showed promising results in small studies, but they were not developed further or tested in larger trials. This section concentrates on systemic immunosuppressive agents that are commonly used in dermatology, such as ciclosporin, systemic steroids, azathioprine, and methotrexate, as well as phototherapy and photochemotherapy. A systematic review of systemic treatments for atopic eczema based on 27 studies including 979 participants was published in 2007 [352]. A further four systematic reviews covering trials of ciclosporin, azathioprine, efalizumab, and desensitization therapy have also provided additional data for this section [352–355].

#### Efficacy

**Systemic steroids** Systemic prednisolone is commonly used in short bursts (a few weeks) in order to get severe atopic eczema into remission. Three older RCTs have suggested that the short-term effect of oral steroids is large in comparison with placebo (Web Table 24.8) [356–358]. Relapse rates were not reported in these studies.

Oral steroids have not been evaluated for more than 4 weeks in atopic eczema. An RCT comparing prednisolone at a dose of 0.5–0.8 mg/kg for 2 weeks followed by placebo for 4 weeks against ciclosporin (2.7–4.0 mg/kg) for 6 weeks had to be stopped prematurely because of a very high drop-out rate due to disease exacerbations, mainly in the prednisolone group. Overall, one out of 21 patients in the prednisolone group achieved stable remission compared with six out of 17 in the ciclosporin group ( $P = 0.031$ ), prompting the authors to conclude that prednisolone is not suitable for inducing a stable remission in severe eczema [359].

**Ciclosporin** The systematic review by Schmitt *et al.* identified 11 studies evaluating the efficacy of ciclosporin in atopic eczema [352], although the other systematic review published around the same time by the same team identified another four studies [253]. Of the 15 studies in the review, which included 602 participants, eight were RCTs (two dose-finding, three double-blind parallel studies, and three crossover studies). Only one trial used an active control – a trial of 30 participants that compared oral ciclosporin against topical tacrolimus, which was inconclusive and confounded by topical corticosteroid use [360]. The general quality of the reporting was poor, except in two studies. The review showed some evidence of publication bias (i.e., larger treatment effects in smaller studies) and the authors suggested caution in interpreting the summary results [253]. The systematic review considered that 12 of the studies were sufficiently similar to allow quantitative pooling of data, and found a clear dose–response effect. At 2 weeks, the overall mean decrease in disease severity was 22% (95% CI, 8–36%) at a dose of 3 mg/kg and 40% (95% CI, 29–51%) for doses of 4 mg/kg and above. After 6–8 weeks of therapy, the mean pooled decrease in severity was 55% (95% CI, 48–62%). Effectiveness appeared to be similar in children and adults, although tolerability might be better in children. There is little doubt that ciclosporin is effective in severe atopic eczema, but it is only useful for short-term treatment because of kidney toxicity.



Figure 24.3 Severe atopic eczema.



**Azathioprine** One crossover RCT of azathioprine (2.5 mg/kg) versus placebo in 37 adults with severe atopic eczema was reported by Berth-Jones *et al.* in 2002 [361]. After 3 months' treatment, those receiving azathioprine had a 26% reduction in disease severity, in comparison with 3% of those on placebo, in an ITT analysis. A subsequent systematic review of unlicensed use of azathioprine for people with severe atopic eczema included 10 studies of 319 patients [353]. Only two of the included studies were RCTs, and both showed decreases in eczema severity compared with placebo. A subsequent RCT of 42 patients with severe atopic eczema comparing azathioprine against oral methotrexate concluded that both drugs reduced severity by a useful amount (42% vs 39% for methotrexate vs azathioprine, respectively) [362], although the trial was too small to demonstrate therapeutic equivalence [363].

**Oral pimecrolimus** One RCT examined the use of three different doses of oral pimecrolimus versus placebo in 103 patients with moderate to severe atopic eczema and found good treatment responses (67% at 7 weeks for the 30 mg twice-daily group) and no signs of nephrotoxicity or hypertension [364].

**Methotrexate, mycophenolate, infliximab, and other biologics** One prospective, open-label study suggested that oral methotrexate is well tolerated and is associated with a sustained reduction in disease activity (55% at 24 weeks) in severe atopic eczema, and suggested that an RCT is now warranted [365]. A subsequent trial of methotrexate versus azathioprine has already been discussed above. The systematic review of systemic therapies describes two uncontrolled studies of mycophenolate mofetil in 20 patients with severe eczema, with a mean decrease in disease activity of 55% and 68% at 8 weeks and 12 weeks, respectively [352]. The authors also reported another small uncontrolled study of infliximab (5 mg/kg) infusions in nine patients, and found that only two patients experienced greater than 50% improvement at 10 weeks [352]. Such uncontrolled studies are difficult to interpret, owing to assessment bias and regression to the mean, especially when patients with severe disease are recruited. A systematic review of efalizumab (a monoclonal antibody that targets T cell activation) found little evidence to support its use [354], and the drug has since been withdrawn owing to the rare but serious adverse effect of progressive multifocal leukoencephalopathy. The use of other biologics in severe atopic eczema is largely speculative [366,367]. One pilot RCT of omalizumab (a monoclonal antibody to IgE) for severe atopic eczema suggested that successful reduction in IgE was not accompanied by clinical benefit [368]. Like the field of psoriasis, several biologics are likely to be developed and tested for severe atopic eczema, and readers should consult the GREAT database for the latest evidence in this rapidly moving field (<http://www.greatdatabase.org.uk/>). Other approaches, such as desensitization immunotherapy, do not appear promising at present [355].

**Phototherapy and photochemotherapy** A total of 11 RCTs were identified, and these are summarized in detail in Web Table 24.9. All but four [369–372] were described in the systematic review by Hoare *et al.* [49]. The quality of reporting in most of the studies was poor. Most studies were underpowered to exclude clinically important differences between different forms of ultraviolet light, with overlapping confidence intervals between the effect estimates of the different groups. It is also unclear to what extent systemic effects may obscure comparisons of two different types of ultraviolet light

used in the same individual – that is, designs that irradiate one half of the body with one type of light and the other half with another type of irradiating light [373]. Broadly speaking, light therapy appears to be very effective in comparison with placebo (using ordinary fluorescent light) for atopic eczema, although it should be noted that tanning compromises blinding in such placebo studies. A subsequent systematic review by Meduri *et al.* summarized just nine trials of ultraviolet light therapy for atopic eczema and concluded that, for acute eczema, ultraviolet A1 (UVA1) appears to be fast and effective and that, for chronic eczema ultraviolet B (UVB) may be more effective, especially for narrowband UVB [374].

A further interesting Norwegian study indirectly assessed the role of ultraviolet light by randomly assigning 30 children to a holiday in the semitropical Canary Islands and 27 at home in cooler Norway [375]. Not surprisingly, the children randomly assigned to the Canary Islands improved more in terms of reduction in eczema scores and quality of life during the holiday, and such an effect was sustained for 3 months after the intervention. It is difficult to separate the effect of ultraviolet light from temperature or sea-water effects, as well as other differences such as diet and psychological effects, between the holiday locations. Nevertheless, the study suggests that a sunny holiday may have a sustained benefit on children with chronic eczema.

### Drawbacks

All of the immunosuppressants currently available carry potentially serious side effects, such as kidney damage (cyclosporin), bone-marrow suppression (azathioprine and methotrexate), osteoporosis (systemic steroids), liver fibrosis (methotrexate), and skin cancer (phototherapy) [49,352]. Long-term effects of oral prednisolone are well known and include hypertension, weight gain, osteoporosis, fat redistribution, diabetes, and acne, although the frequency of such complications when the treatments are used for a few weeks or months to gain control in severe atopic eczema is unknown [49]. The systematic review of cyclosporin found that adverse effects such as gastrointestinal upset occurred in around 40% of patient-months described in 15 studies [253]. An increase in baseline serum creatinine over 30% was found in 115 of patients, hypertension in 6%, and infections in 12% of patients [376]. Kidney damage can occur within a year of cyclosporin treatment and be permanent [377]. Treatment appeared to be better tolerated in children, although this may be partly due to larger doses being used in adults. For azathioprine, bone-marrow toxicity may be minimized by assessing blood thiomethylpurine transferase activity beforehand, although the test may not be widely available. In the RCT of azathioprine, 16 of the 37 participants withdrew (12 when on azathioprine and two on placebo), 14 developed gastrointestinal disturbance, two developed leukopenia, and eight had abnormal liver function tests [361].

Although the one RCT of oral pimecrolimus found minimal side effects (one patient in the placebo group had chest and abdominal pain, an abnormal electrocardiogram, and sinus bradycardia; and one patient in the pimecrolimus group had elevated fasting plasma glucose levels) [364], concerns associated with carcinogenicity in animals have prevented this form of therapy from becoming more widely available [185]. More data are needed on methotrexate, azathioprine, mycophenolate, and biologics in atopic eczema, as the numbers treated so far with these agents are far too small for it to be claimed that they are safe in either the short term or long term.

The short-term drawbacks of ultraviolet therapy include burning and itching, and they can usually be overcome by light testing before therapy and the use of emollients after treatment. Some

people find ultraviolet cabinets claustrophobic, and some very young children find the experience frightening. The long-term effects of giving ultraviolet light to young children with atopic eczema in terms of melanoma and non-melanoma skin cancer are unknown [49], and caution should be taken when extrapolating guidance based on adults receiving photochemotherapy for psoriasis, especially since susceptibility to melanoma may be enhanced in childhood.

### **Clinical implications**

Both ultraviolet light and systemic treatments such as short courses of ciclosporin are probably useful and safe in the person depicted in the case scenario. The choice of treatment would be largely determined by the person's preferences and local availability of treatment. Safety is a factor limiting the long-term use of all of these agents. Planned short-term use (2–3 months) to try to obtain a remission or give the person a “holiday” from severe symptoms seems a reasonable option, resorting to topical treatments such as intermittent use of potent topical steroids or tacrolimus once control is achieved. It is unclear at this stage whether different genetic subtypes of atopic eczema (e.g., those with a major barrier defect as determined by mutations in the filaggrin gene [378]) respond differently to different systemic treatments. Future trials should consider biomarker-based stratification using genetic or other biologic markers for disease-modifying strategies [40], or strategies that interfere with development of autoimmunity which may contribute to the chronicity of severe atopic eczema [379].

#### **Key points: systemic immunosuppressive therapy**

- There is reasonable RCT evidence to support the use of oral ciclosporin for severe atopic eczema.
- Kidney damage limits the long-term use of ciclosporin to a few months, with a return to conventional topical treatment once control is maintained.
- There is some evidence that both azathioprine and methotrexate are effective for the control of severe chronic atopic eczema, but the evidence base is still relatively small and short term, and both drugs require careful monitoring.
- One trial has shown that oral pimecrolimus was beneficial in moderate to severe atopic eczema, but oral pimecrolimus is not licensed because of concerns about the possible long-term development of lymphomas.
- RCTs on other potentially useful treatments, such as mycophenolate or biological therapies in patients with atopic eczema, are still lacking.
- Phototherapy (e.g., UVA1 for acute eczema and narrowband UVB for chronic eczema) has consistently been shown to be beneficial in atopic dermatitis, but both are limited by the long-term risk of skin cancer after many treatments.
- There is an urgent need for studies that compare systemic therapies against each other rather than against placebo for people with severe atopic eczema.
- There is a need for longer term studies of systemic immunosuppressive treatment for atopic eczema, in order to evaluate long-term safety and whether the use of these agents alters the natural history of the disease.

### **General summary observations on the evidence base for atopic eczema**

- Although around 600 RCTs have been conducted for atopic eczema, their ability to inform us about the everyday management of patients is still limited.
- Many people with atopic eczema are treated in the community, yet community-based trials are very rare in this field.
- Most of the trials of people with atopic eczema have reflected the agenda of the drug industry.
- New drugs have often been only compared against placebo in trials, rather than being compared against existing active treatments, which makes it difficult for clinicians and patients to decide which is best. Independent comparative effectiveness research is needed in order to make head-to-head comparisons.
- Some of the limitations of the atopic eczema evidence base are due to a generally poor quality of study reporting. All dermatology journals have a role to play by insisting on the basic standard of clinical trial reporting, as outlined in the Consolidated Standards of Reporting Trials 2010 statement (<http://www.consort-statement.org>).
- All future clinical trials in atopic eczema should be registered prospectively before recruitment starts in order to minimize selective reporting outcome bias and publication bias.
- Outcome measures used in atopic eczema trials are a bit of a mess, characterized by a profusion of poorly developed and unvalidated scales, making comparisons across studies difficult. Investigators should stick to using the core outcome sets recommended by the international HOME group (<http://www.homeforeczema.org/>).
- Some interventions (e.g., topical steroids and topical calcineurin inhibitors) are well supported by RCT evidence.
- For other interventions (such as Chinese herbs and house dust mite reduction), there is simply insufficient evidence to decide whether they are effective; better research is needed.
- In some areas (e.g., topical steroid–antibiotic combinations), the RCT evidence does not support a clinically useful effect – providing dermatologists and patients with an opportunity to disinvest in such treatments.
- In most people with mild to moderate atopic eczema, the condition can be easily controlled with a combination of emollients and topical corticosteroids for inflammatory flares.
- In those with more troublesome atopic eczema, proactive treatment with weekly topical corticosteroids or topical calcineurin inhibitors appears to have a large impact on prevention of flares.
- Cheap and well-established systemic agents such as oral steroids or azathioprine or methotrexate should be compared against each other in people with severe atopic eczema in large pragmatic trials.
- There is still room for more safe and effective treatments for severe atopic eczema.
- Trials exploring disease prevention need to be conducted for atopic eczema.
- Larger studies need to be conducted in order to explore subgroup differences for different subtypes of eczema – or example, patients who are atopic, those with associated asthma, and those with filaggrin gene mutations.

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Web tables referred to in this chapter are published on the book's website (<http://www.evidbasedderm.com>).



### Website tables

Web Table 24.1 Emollients for the treatment of atopic eczema.

Web Table 24.2 Topical steroids versus placebo in atopic eczema: results of RCTs.

Web Table 24.3 Oral antihistamines for atopic eczema.

Web Table 24.4 RCTs of dust mite reduction for the treatment of atopic eczema.

Web Table 24.5 Table of elimination diets in the treatment of those with established atopic eczema.

Web Table 24.6 Randomized controlled trials of probiotics in the treatment of atopic eczema.

Web Table 24.7 Randomized controlled trials that have evaluated treatments for clinically infected atopic eczema.

Web Table 24.8 Randomized controlled trials that have evaluated antiseptics for atopic eczema.

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## CHAPTER 25

# Seborrheic dermatitis

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## Background

### Definition

Seborrheic dermatitis is a chronic inflammatory skin disease characterized by erythematous and scaling plaques, with a distinctive distribution in scalp, eyebrows, nasolabial folds, retroauricular regions, sternum, and between the shoulder blades (Figure 25.1) [1], areas rich in sebaceous glands.

The relationship with “dandruff” is unclear; and this is a more generic term that refers to scalp flaking, regardless of etiology [2]. Pruritus of the scalp is often associated with the condition.

### Incidence/prevalence

There are two forms of seborrheic dermatitis: an infantile and an adult form. The former is self-limited and confined to the first 3 months of life, and the latter is chronic, peaking between the ages of 30 and 50 years. The prevalence of adult seborrheic dermatitis is estimated at 5% [3].

In a group of male adolescents (2201) in Brazil, the global prevalence of scalp seborrheic dermatitis has been found to be 11% and the occurrence was associated with higher body fat content [4].

In acquired immunodeficiency syndrome (AIDS) patients the incidence is increased (30–80%), probably related to CD4 levels (altered immune surveillance) [5].

Oble *et al.* have characterized an animal model which may mimic the seborrheic dermatitis in AIDS [6], implicating a fungal organism and CD4<sup>+</sup> T cell lymphopenia.

### Etiology/risk factors

The etiology is not clear, and several factors could play a major role: sebaceous gland secretions, individual susceptibility, and microfloral metabolism. Qualitative and quantitative abnormalities in the composition of sebum have been suggested, but not clearly defined. Dandruff and seborrheic dermatitis are chronic scalp manifestations probably with similar etiology, differing in severity. The manifestations are related to superficial stratum corneum disorders, including alterations of the epidermis with hyperproliferation, excess lipids, interdigitation of the corneal envelope, and parakeratosis [7]. The nonpathogenic fungus *Malassezia furfur* (*Pityrosporum ovale* and *Pityrosporum orbiculare*) may play a role [8], but the mechanism has not been completely clarified.

*Malassezia* strains are isolated more often from unhealthy scalps than from the scalps of normal individuals even though the total frequency is relatively low. However, several other fungal species have been isolated that are significantly different from those on healthy scalp, suggesting that the skin microbiome is modified during seborrheic dermatitis [9].

Investigations on the role of these pathogens have focused on their lipid metabolism. *Malassezia restricta* and *Malassezia globosa* require lipids and are capable of degrading sebum, releasing free fatty acids from triglycerides, consuming specific saturated fatty acids, and leaving behind the unsaturates. Penetration of the modified short fatty acids results in inflammation and irritation. The phospholipase activity, and particularly its induction after  $\beta$ -endorphin exposure, is a distinct metabolic trait of *Malassezia* strains isolated from lesional skin of seborrheic dermatitis patients, suggesting that the activity of this enzyme could be the target of additional research. The production of bioactive indoles such as *malessezin* has been related to the pathogenesis of the manifestation. The bioactive indoles are potent ligands of the aryl hydrocarbon receptor (AhR) expressed by keratinocytes and dendritic cells and are capable of inducing an inflammatory reaction and modulating the immune response [10].

Some studies have hypothesized that seborrheic dermatitis is related to altered immune response to *M. furfur*.

A transcriptomic analysis of scalp biopsies from individuals with dandruff/seborrheic dermatitis revealed more than 70 probes are differently regulated, with significant induction of inflammatory genes and proteins and conversely repressed lipid metabolism genes [11].

Increased keratinocyte and sebocyte turnover has been reported in association with altered keratinization. Systemic lipid metabolism and antioxidants may play a role in modulating the disease onset and the inflammatory reaction. A few studies have linked the onset or relapses with the patient's psychological condition, alcohol intake, psychotropic drugs, and a deficiency of micronutrients (lithium, zinc, magnesium, biotin).

### Prognosis

Although there are many treatments for seborrheic dermatitis, recurrences are very common, with the disease typically relapsing for years. Although the prognostic studies identified were not



Figure 25.1 A patient with seborrheic dermatitis.

long-term ones, preventive regimens have been developed to reduce the severity of the disease, including improvement in lifestyle, intake of supplements, and sun exposure.

### Aims

The aims of the treatment are to reduce symptoms and relapses with short-term treatment.

### Outcomes

No standard scales were found for the assessment of the severity of seborrheic dermatitis. Outcomes include the severity of symptoms (erythema, desquamation, itching), the rate of recurrence, the number of *P. orbiculare* colonies, patient satisfaction, and cosmetic acceptability.

### Search methods

Since few randomized controlled trials (RCTs) were found that met the criteria for clinical evidence, observational studies were included (up to September 2012).

## Questions

### What are the effects of topical treatment?

#### Antifungal agents

Topical antifungals are well established in the treatment of seborrheic dermatitis, and several clinical trials showed that different topical antifungal agents improve seborrheic dermatitis.

#### Efficacy

No systematic reviews were found.

**Ketoconazole** Seven double-blind placebo-controlled trials used cream or shampoo [12–18]. The largest trial, using 2% keto-

conazole shampoo ( $n = 575$ ) reported an excellent response in 88% of the patients treated. The treatment was effective in preventing relapses when used prophylactically once a week [12]. An RCT comparing 2% ketoconazole shampoo with 2.5% selenium sulfide shampoo found that ketoconazole was statistically superior to selenium sulfide ( $P = 0.0026$ ) and was better tolerated [13]. In two double-blind crossover studies ( $n = 20$  and  $n = 35$ ), the change in the clinical score with ketoconazole shampoo was significant ( $P < 0.01$ ) [14,15]. Two RCTs demonstrated the clinical efficacy of 2% cream in comparison with a placebo [16,17]. In a double-blind placebo-controlled trial, a gel containing a combination of 2% ketoconazole and 0.05% desonide was superior to the unmedicated gel [18].

One open, randomized, parallel study including a total of 66 patients showed that a 2% formulation was significantly more effective than a 1% formulation ( $P < 0.001$ ) and that the intermittent application of 2% ketoconazole shampoo can successfully prevent relapse [19].

The safety of 2% ketoconazole shampoo is supported by absorption studies and by local irritancy and contact sensitivity studies. Ketoconazole shampoo does not influence sebum production, but improves its delivery onto the skin surface [20].

**Bifonazole** We found three double-blind controlled trials and two open studies [21–23]. The largest, involving 100 patients, reported that 1% bifonazole cream was significantly better than placebo ( $P < 0.05$ ) [21].

**Ciclopiroxolamine** One placebo-controlled double-blind study of ciclopiroxolamine 1% cream in facial seborrheic dermatitis (57 patients in the ciclopiroxolamine group and 72 in the vehicle group) found a statistically significant difference ( $P < 0.01$ ) between the two treatment groups at the end of the initial phase (twice daily for 28 days) and in the maintenance phases (once daily for 28 days) [24].

We found five randomized, double-blind, vehicle-controlled trials of ciclopirox shampoo. In one study ( $n = 203$ ), the most pronounced improvement in the treatment of seborrheic dermatitis of the scalp was seen with ciclopirox 1% shampoo, in comparison with the lowest concentrations (0.1% and 0.3%) and the vehicle [25]. A trial ( $n = 183$ ) compared different application frequencies of 1% ciclopirox shampoo [26]. The most pronounced improvement was seen in the group treated three times a week and twice a week, in comparison with once a week and vehicle shampoo. Another study ( $n = 499$ ) reported that an effective treatment response was achieved in 26% of patients treated with ciclopirox in comparison with 12.9% of patients treated with the vehicle [27]. Vardy *et al.* ( $n = 102$ ) showed that the improvement of seborrheic dermatitis was significantly greater in a group treated with ciclopirox than in a group treated with placebo (93% and 41%, respectively) [28].

In a large study, 949 patients were randomly assigned to receive 1% ciclopirox shampoo once or twice weekly or vehicle for 4 weeks [29]. Ciclopirox once and twice weekly produced response rates of 57.9% and 45.4%, respectively, in comparison with 31.6% for the vehicle.

**Terbinafine** We found two RCTs: in one, the lesions cleared in 11 of 18 eligible patients after treatment with 1% terbinafine solution once daily for 4 weeks [30], while the other study



reported complete remission in 10 of 35 patients treated with 1% terbinafine cream [31].

**Other antifungals** Beneficial effects have been reported in open studies with fluconazole [32] and fenticonazole [33]. One study in a group of 30 men demonstrated that 0.2% octopirox in a shampoo vehicle was superior to the same level in the simple shampoo base and equivalent in activity to a much higher level (0.5%) in the base only [34].

#### **Drawbacks**

The few adverse effects reported include erythema, dryness, and pruritus.

#### **Comment**

The various antifungal drugs have not been compared. The possible mechanisms of action of these compounds include antifungal and anti-inflammatory effects.

#### **Zinc pyrithione**

A meta-analysis on nine different clinical trials confirmed a slight (20%) but significant improvement of symptoms with the use of a shampoo containing zinc pyrithione with no difference in the rate of the response among gender or ethnicity [35]. The transcriptome of dandruff/seborrheic dermatitis after treatment revealed that the treatment produced a profile resembling those of healthy scalp skin [11].

#### **Corticosteroids**

Recently, little information has been published on the use of topical steroids. The drugs, applied for 1–4 weeks, improve seborrheic dermatitis and do not cause systemic effects, but relapses are more frequent than with topical antifungals.

#### **Efficacy**

No systematic reviews were found. In one RCT, a 1% hydrocortisone solution was compared with miconazole and a combination of miconazole and hydrocortisone in 70 patients [36]; the combination was most effective. Recurrences were seen most frequently in the hydrocortisone group. We found one randomized double-blind controlled trial of 2% ketoconazole cream versus 0.05% clobetasol 17-butyrate cream [37], and one trial comparing topical application of 0.02% flumethasone pivalate with 2% eosin in 30 infants with seborrheic dermatitis; in the latter study, the two treatments were found to have comparable effects [38].

In an RCT study, clocortolone pivalate 0.1% cream was a more effective therapy than vehicle, and the patients had a low rate of adverse events [39].

#### **Drawbacks**

Long-term corticosteroid therapy may induce adverse effects, such as skin atrophy and telangiectasia.

#### **Comment**

No recent RCTs have demonstrated the efficacy of corticosteroids, although they are used as comparative drugs.

#### **Lithium succinate**

RCTs have found that lithium succinate improves seborrheic dermatitis in comparison with placebos.

#### **Efficacy**

We found two randomized, double-blind, placebo-controlled trials and one open trial with 8% lithium succinate ointment [40–42]. One crossover trial in nine centers (200 patients) and a parallel-group study in two centers (27 patients) showed that the symptom score improved significantly in the lithium group ( $P < 0.0001$ ) [40]. The other double-blind trial, conducted in 12 patients with AIDS-associated seborrheic dermatitis, reported rapid (2–5 days) and significant ( $P < 0.01$ ) clinical improvement in patients treated with lithium succinate [41].

#### **Drawbacks**

Adverse effects consisted of skin and eyelid irritation in a few patients.

#### **Comment**

Lithium inhibits growth in small colony strains of *Pityrosporum* and blocks the release of free fatty acids from tissue. Lithium also has potentially anti-inflammatory actions.

#### **Antibacterials**

We found only a few studies on metronidazole.

#### **Efficacy**

No systematic reviews were found. A double-blind study ( $n = 44$ ) described significant improvement after the use of 1% metronidazole gel in comparison with a placebo for 8 weeks. Fourteen patients in the metronidazole group and two in the placebo group had complete improvement [43].

#### **Drawbacks**

None reported. Metronidazole gel was well tolerated and did not produce adverse effects.

#### **Comment**

The mechanism of action of metronidazole is not known.

#### **Benzoyl peroxide**

Two controlled studies have reported on the efficacy of benzoyl peroxide.

#### **Efficacy**

Of the two studies, one open trial noted improvement in 28 of 30 patients treated for several months with 2.5% benzoyl peroxide [44]. The second, a double-blind RCT including 59 patients, compared 5% benzoyl peroxide with placebo for 4 weeks and reported a significant improvement in erythema, pruritus, and scaling in the group treated with benzoyl peroxide ( $P < 0.05$ ) [45].

#### **Drawbacks**

Skin irritation was reported as a side effect.

#### **Propylene glycol**

We found one double-blind controlled study, in which 39 patients with seborrheic dermatitis of the scalp were treated with a solution containing 15% propylene glycol [46]. The lesions improved in 89% of the patients treated with propylene glycol, in comparison with 32% in the placebo group. In vitro, the *P. orbiculare* counts were reduced significantly after treatment with propylene glycol, but not in the placebo group.

## Pimecrolimus

RCTs have found that pimecrolimus cream 1% improves seborrheic dermatitis.

### Efficacy

In one study ( $n = 19$ ), 1% pimecrolimus cream was applied as monotherapy twice daily for 7 days and for an additional period of 7 days until complete clearance was achieved [47]; 52% of patients reached complete clearance.

We found one open-label clinical trial conducted in 20 patients – 11 patients in the 1% pimecrolimus cream group and nine patients in the betamethasone 17-valerate 0.1% cream group [48]. Both agents were highly effective in the treatment of seborrheic dermatitis. More severe and frequent relapses were observed with betamethasone than with pimecrolimus.

### Drawbacks

Rosaceaform dermatitis is an adverse side effect complicating treatment with 1% pimecrolimus cream [49].

### Comment

Pimecrolimus is a calcineurin inhibitor that has been successfully used in inflammatory skin diseases. It selectively targets T cells and mast cells and inhibits T cell proliferation and the production and release of interleukin-2, interleukin-4, interferon gamma, and tumor necrosis factor- $\alpha$ . In contrast to corticosteroids, pimecrolimus does not induce skin atrophy.

## Miscellaneous

Several treatments have been claimed to be effective in uncontrolled studies. A blind, randomized, parallel-group study in 80 patients found that 1% ichthylol (ichthammol) was superior to 4% coal tar in seborrheic dermatitis of the scalp [50].

Tacalcitol (1 $\alpha$ ,24-dihydroxycholecalciferol) was used in four patients, with good results [51]; crude honey (30 patients) [52], borage oil, 40% urea ointment [53], dithranol (18 patients) [54], pyridoxine, and cystine [55] have been reported to be beneficial in uncontrolled studies.

## Ultraviolet light

RCTs have found that phototherapy improves seborrheic dermatitis.

### Efficacy

No systematic reviews were found. Limited evidence suggests that natural sunlight has a significant effect on seborrheic dermatitis [56,57]. One RCT ( $n = 48$ ) found improvement in 85% of patients receiving selective ultraviolet phototherapy, and in 76% of patients treated with psoralen–ultraviolet A after a mean of 26 treatments [58]. In an open study, 18 patients with severe seborrheic dermatitis were treated with narrowband ultraviolet B (UVB; TL-01) phototherapy, three times weekly, starting with 70% of the minimal erythema dose up to a maximum of 8 weeks. All patients responded to narrowband UVB. Twelve completed the study; six had complete remission and six had marked improvement [59].

### Drawbacks

No side effects were reported, except for rare episodes of moderate erythema.

### Comment

The trials of phototherapy were too few for its effectiveness to be evaluated.

## What are the effects of systemic treatments?

### Antifungal drugs

We found limited evidence that oral antifungals are beneficial.

### Efficacy

We found no systematic reviews.

**Ketoconazole** One double-blind placebo-controlled crossover study in 19 patients compared ketoconazole 200 mg/day for 4 weeks with placebo. Seventy percent of the patients showed significantly greater improvement with ketoconazole, particularly on the scalp, in comparison with 10% with placebo ( $P < 0.01$ ) [60].

**Terbinafine** In one placebo-controlled trial ( $n = 60$ ), oral terbinafine 250 mg once daily for 4 weeks significantly reduced scores ( $P < 0.0001$ ) in comparison with the baseline and with control groups [61].

In a randomized, double-blind, placebo-controlled study ( $n = 174$ ) in patients with lesions in nonexposed sites and in patients with lesions in exposed skin areas, oral terbinafine (250 mg/day) or a placebo were each administered for 6 weeks [62]. In patients with lesions in nonexposed sites, the response rate was significantly higher with terbinafine (70% vs 45.4%;  $P = 0.03$ ). No significant differences were reported in patients in exposed skin areas.

**Itraconazole** We found two RCTs of oral itraconazole. In one ( $n = 32$ ), the treatment was given in two different periods. In the first period, 1% hydrocortisone cream was administered for 4 weeks and 200 mg itraconazole daily during the first week; in the second period, the cream was discontinued and itraconazole was given on the first 2 days of every month for 11 months [63]. Nineteen patients showed significant improvement or complete recovery, six had moderate improvement, and three had slight improvement. In an open, noncomparative trial ( $n = 29$ ), itraconazole 100 mg was given twice a day for 1 week and then, after a 3-week interval, for the first 2 days of the following 2 months [64]. Clinical improvement was observed in 23 patients. In another study itraconazole was given to 30 patients in a dose of 100 mg twice daily for 1 week followed by 200 mg/day for first 2 days of the following 2 months. Clinical improvement was observed in 83.3% cases [65].

### Drawbacks

Ketoconazole damages the liver and interferes with testosterone metabolism. No side effects were reported during the terbinafine studies.

### Comment

Seborrheic dermatitis relapses when the drugs are stopped, so that prolonged treatment is often needed. Systemic antifungal drugs are not suitable for this.

## What are the effects of nutrients?

We found no controlled studies of the effects of nutrients, vitamins, and trace elements on seborrheic dermatitis. On the basis of limited

observational evidence, seborrheic dermatitis is said to have improved after administration of vitamins A, E, D, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, and C, niacin, biotin, selenium, zinc, or iron [66,67].

## Do treatments that reduce sebaceous secretions improve the symptoms?

### Retinoids and antiandrogens

We found that few drugs interfere with sebum secretion, and there is insufficient evidence that controlling sebum production leads to improvement of seborrheic dermatitis.

### Efficacy

Oral retinoids reduce sebaceous gland size, suppress sebum production, and inhibit sebocyte differentiation; they also have anti-inflammatory activity [68]. Antiandrogen and 5- $\alpha$ -reductase inhibitors reduce the size of the sebaceous glandular lobules and ducts [69].

We found no evidence to support the hypothesis that reducing sebum production decreases the probability of developing seborrheic dermatitis.

### Key points

- RCTs show that topical antifungal treatment and metronidazole are effective.
- Limited evidence suggests that systemic antifungal therapy can be useful in controlling the disease.
- Few RCTs have examined the efficacy of topical steroids.
- We found limited or no evidence on the effect of natural sunlight and/or systemic nutrients.

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# Treatment of psoriasis<sup>1</sup>

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## Background

### Definition

Psoriasis is an inflammatory disease of the skin characterized by an accelerated rate of epidermal turnover, with hyperproliferation and defective maturation of epidermal keratinocytes. In the majority of cases psoriasis is a chronic disease, which in its most common form – chronic plaque psoriasis – manifests as well-demarcated, often symmetrically distributed, thickened, red, scaly plaques. These may vary considerably both in size and in number and may involve any part of the skin, although they are found most typically on the extensor surfaces of the knees and elbows, in the sacral area, and in the scalp. Appearances may be modified by the site of involvement, with flexural areas showing beef-red shiny plaques without scale (flexural or inverse psoriasis), palms and soles showing marked hyperkeratosis and fissuring, and nails becoming distorted by thimble-pits, thickening, and nail-plate detachment. Up to 8% of individuals with psoriasis may have an associated inflammatory arthropathy [1], which in severe cases may be the dominant cause of morbidity.

Acute inflammatory forms of psoriasis may develop *de novo*, or may complicate existing chronic plaque psoriasis. Acute guttate psoriasis characteristically affects children and young adults following streptococcal infection [2]. Typically, showers of tiny red papules (likened to raindrops or guttate) erupt over large areas of the skin surface 1–2 weeks after an episode of acute streptococcal pharyngitis or tonsillitis. Erythrodermic and generalized pustular psoriasis are uncommon but severe and potentially life-threatening forms of psoriasis, which may be complicated by high-output cardiac failure, temperature dysregulation, and septicemia, particularly in the elderly.

Psoriasis is associated with two relatively uncommon conditions that may cause long-lasting disability as a result of severe inflammation and pustulation affecting the hands and feet. The first is now more commonly referred to as palmoplantar pustulosis, but is still widely known as chronic palmoplantar pustular psoriasis. Although

associated with psoriasis elsewhere in about one-fifth of cases, it is now considered to be a genetically separate entity [3]. Acropustulosis (acrodermatitis continua of Hallopeau), on the other hand, may be associated with generalized pustular psoriasis [3]. The relationship of these two conditions to psoriasis vulgaris remains poorly understood.

### Prevalence

Psoriasis affects 1–3% of the general population. It is believed to be less frequent in some ethnic groups (e.g., in people from West Africa and China), but we have found no reliable epidemiological data to support this [4].

### Etiology

Epidermal turnover is greatly accelerated in psoriasis, such that keratinocytes within active psoriatic plaques may travel from the basal layer of the epidermis to the stratum corneum in as little as 4 days, rather than the normal 28 days. Exactly what drives this process is incompletely understood, but it is agreed that it is mediated by activated T lymphocytes and that there is a strong genetic component [5]. Physical trauma, acute infection, and some medications (e.g., lithium and beta-blockers) are believed to trigger the condition. A few observational studies have linked the onset or relapse of psoriasis with stressful life events and personal habits, including cigarette smoking and, less consistently, alcohol consumption. An association of psoriasis with body mass index is also well documented [4].

### Prognosis

Psoriasis is known to last years or decades and to be subject to periods of remission and relapse. We did not, however, find any long-term studies examining the prognosis. There is growing evidence that moderate to severe psoriasis is associated with a significantly increased risk of cardiovascular morbidity [6,7], with at least double the prevalence of obesity, type 2 diabetes, arterial hypertension, hyperlipidemia, and coronary heart disease [7]. The odds of having the metabolic syndrome, a defined combination of these conditions, were found to be more than five times higher amongst 581 adult patients hospitalized for severe psoriasis than in a control group of hospitalized patients (odds ratio [OR], 5.29) [7]. Psoriasis

<sup>1</sup>Based on Chapter 21 from the second edition by Luigi Naldi and Robert J.G. Chalmers.

may substantially affect quality of life, by influencing a negative body image and self-image and limiting daily activities, social contacts, and work. One systematic review (search date 2000, 17 cohort studies) confirmed that severe psoriasis is associated with lower levels of quality of life than mild psoriasis [8]. At present, there is no cure for psoriasis. However, in many people it can be well controlled with treatment, at least in the short term.

### Aims of treatment

Until there is a safe and effective cure for psoriasis, a balance needs to be struck between patients' individual perceptions of disability from psoriasis, their willingness to devote time and effort to managing the disease, and their preparedness to accept risks from treatment.

In a European consensus group, treatment goals have been defined to give guidance on the assessment of a treatment success. According to the consensus group, a treatment can be considered a success and should be continued as a maintenance therapy if the improvement of the psoriasis area and severity index (PASI) is equal to or more than 75% within a time period of 16–24 weeks. Treatment regime should be modified if improvement of PASI is less than 50%. In a situation where the therapeutic response improved by equal to or more than 50% but by less than 75% as assessed by PASI, the therapy should be modified if the dermatology life quality index (DLQI) is  $>5$  but can be continued if the DLQI  $\leq 5$  [9].

### Relevant outcomes

Outcomes should reflect the aims stated above: efficacy as measured by many different outcome measures like PASI, physician global assessment (PGA), or some other objective disease activity score, disease-related quality of life; patient satisfaction and autonomy, clearance or improvement of psoriasis over time; acceptability to patients of treatment regimens; duration of remission; and adverse effects of treatment, number of drop outs due to side effects, management and control of comorbidities. Harmonizing outcome measures used in clinical studies and practice may improve the comparability of treatments in the future (<http://www.comet-initiative.org>).

### Methods of search

This chapter uses information extracted from different systematic reviews and evidence-based guidelines. It was generally attempted to use information from the most recent sources available. The sources used are stated at the beginning of the individual section. In some cases, additional important trials published after the deadline of the cited reviews were added. The description of "harms" is done by means of a narrative selection of information derived from the guidelines and additional clinical trials. Very rare adverse events are not likely to have been identified in clinical trials.

## Topical treatment of chronic plaque-type psoriasis

### How effective are different topical treatments for chronic plaque-type psoriasis?

#### Sources of information

- The National Institute for Health and Clinical Excellence (NICE) National Clinical Guideline Centre. Psoriasis, Management of Psoriasis, Clinical Guideline, October 2012 (search date March

- 8, 2012, Medline, Embase, Cochrane, Cumulative Index to Nursing and Allied Health Literature (CINAHL)) [10];
- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11];
- Cochrane review on topical treatments for chronic plaque psoriasis 2009 (search date 2005, Medline, Embase, Science Citation Index, Biosis, Dissertation Abstracts, Inside Conferences; SIGLE; National Research Register, metaRegister of Current Controlled Trials) [12];
- Menter *et al.*: Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies (search date 2008, Medline) [13].

### Calcineurin inhibitors

#### Benefit

**Global estimate of efficacy** In 40–50% of patients tacrolimus shows a significant improvement or complete clearance after 6–12 weeks. Pimecrolimus has not been studied in a randomized controlled trial (RCT) in chronic plaque-type psoriasis [11].

**Different dosages of calcineurin inhibitors** Tacrolimus 0.1% ointment is the most commonly used concentration and is preferable in psoriasis [11–13]. One psoriasis study applied tacrolimus 0.3% gel and one used a 0.5% cream. Tacrolimus 0.03% ointment has not been studied in RCTs in psoriasis.

**Tacrolimus versus placebo** There are no true placebo-controlled trials for tacrolimus ointment in psoriasis. In one trial, the combination of topical tacrolimus 0.1% plus 6% salicylic acid gel is compared with salicylic acid gel alone demonstrating an improvement of at least 75% in 11/24 patients compared with 4/24 in the control group [11].

**Calcineurin inhibitors versus vitamin D analogues** Two trials compared topical tacrolimus with calcipotriol. In the first study, tacrolimus 0.3% gel and 0.5% cream and calcipotriol were equally effective (about 45% had a PGA of "much better") [11]. In a second study, 50 patients with facial and anogenital chronic plaque-type psoriasis, 60% of patients in the tacrolimus group were completely clear compared with 33% in the calcipotriol group. The Cochrane review by Mason *et al.* demonstrated no significant difference between tacrolimus and vitamin D3 derivatives (mean,  $-0.04$  [ $-0.53, +0.61$ ]) [12].

**Calcineurin inhibitors in combination therapy** There are no RCT studies on combination therapy in chronic plaque-type psoriasis with other topical or systemic therapies. Combination therapy with ultraviolet (UV) therapy should be avoided because of a potential carcinogenic effect.

#### Harms

It should be noted that all information available is derived from their use in atopic dermatitis. Most people experience a burning sensation immediately after applying tacrolimus and to a lesser extent for pimecrolimus, which often diminishes after a couple of days [11–13]. Application of a topical corticosteroid (TC) may reduce the burning sensation. The immunosuppressive effects of calcineurin inhibitors (CNIs) leads to an increased risk of bacterial and viral skin infections (e.g., folliculitis, warts, herpes simplex). A

combination with UV therapy (or excessive sunlight exposure) should be avoided because animal models have suggested an increased risk of cutaneous malignancies [11–13]. No data are available on the carcinogenic effect of CNIs in humans, but both CNIs have a “black box” warning [13]. Although there are no reports on birth defects related to exposure to CNIs, use of this drug class during pregnancy should be avoided. There are no known drug interactions.

### Comments

Topical tacrolimus (or pimecrolimus) is not the first-line treatment for chronic plaque-type psoriasis, but may be considered for facial, intertriginous, and anogenital regions because of adverse effects of corticosteroids and vitamin D analogues [11–13]. Since tacrolimus ointment is off label for psoriasis, it is recommended to document its use carefully. The tacrolimus 0.1% ointment is preferable, but its vehicle may not be cosmetically acceptable for patients.

### Dithranol

Throughout this section, the individual studies referred to can be found in Refs [11–13].

### Benefit

**Global estimate of efficacy** The response rate (significant improvement or complete clearance) for dithranol varies greatly between 30 and 70% (evidence level 2) [11,13].

**Different dosages of dithranol** Outpatient treatment is preferably performed with short-contact therapy. A 1% cream is applied for 10 min once daily and gradually the duration of contact is increased up to 30 min after which the concentration can be increased up to 3% [11]. The cream should be rinsed off without soap using lukewarm water. “Classical” dithranol therapy begins with 0.1% ointment twice daily without washing it off. Depending on the level of irritation, the concentration is doubled every 3 days up to 1–3%.

**Dithranol versus placebo** In the two small placebo-controlled studies of the efficacy of dithranol as monotherapy for 12 and 27 patients, a totally aqueous gel formulation of dithranol in increasing concentrations as tolerated up to as high as 2% applied twice daily for 4 weeks, and a 1 min treatment with 2% dithranol ointment daily for 3 weeks both demonstrated significantly better results than placebo in the treatment of psoriasis [13]. The Cochrane review by Mason *et al.* included three studies on topical therapy of psoriasis vulgaris with dithranol [12]. With a 95% confidence interval (CI) of –0.46 to –1.65 the mean (standardized weighted mean difference) for comparison of efficacies of verum versus placebo is at –1.05, clearly in the significant range, and thus is evidence of the efficacy of local dithranol therapy.

**Classic dithranol versus short contact** The available data failed to show the superiority of classic therapy over short-contact therapy [11]. Moreover, the modern preparation was equally effective compared with the traditional dithranol preparations [11].

**Dithranol versus vitamin D analogues** Monastrili *et al.* showed that each of the 23 patients using short-contact dithranol therapy reached PASI 75, but none of the patients achieved PASI 100 after 6 weeks. However, adding calcipotriol twice daily to this regimen resulted in complete clearance of all patients in the comparative arm. Van de Kerkhof *et al.* showed that short-contact dithranol was

superior to calcipotriol after 12 weeks (63.8% vs 58.5% PASI reduction), but not after 4 weeks [11].

The Cochrane review by Mason *et al.* demonstrated no significant difference between dithranol and vitamin D3 derivatives (mean, –0.04 [–0.53, +0.61]) [12].

**Dithranol versus topical steroids** One trial compared dithranol monotherapy with clobetasol and a combination of both. Each monotherapy resulted in a remission of 80% and the combination therapy in complete remission of all treated plaques [11,13].

**Dithranol in combination therapy** As mentioned above, dithranol can effectively be combined with calcipotriol and topical steroids. Its combination with phototherapy will be discussed in that section.

### Harms

The most common adverse effects are redness and burning of (peri) lesional skin and guide the increment of contact duration and concentration. Brown discoloration of the skin, nails, hair, and clothing can occur. The discoloration of the skin usually persists for 4–6 weeks. These side effects can be prevented by using glove when applying the drug, avoiding use of dithranol on the face (and intertriginous areas), protecting the surrounding skin (e.g., zinc paste), or by applying topical steroids. Nevertheless, these cosmetic adverse effects have decreased the use of dithranol over the years.

Blistering and necroses may occur due to overdoses. Very rarely a contact allergy can develop.

Although there are no reports on birth defects related to dithranol exposure, use of dithranol should be restricted to small areas (<30% of body surface area (BSA)) during pregnancy. During nursing it should not be applied on the breasts. There are no known drug interactions.

### Comments

The feasibility of dithranol in an outpatient setting is limited because of side effects, but it is effective in day-care centers or during hospitalization and can be combined with other topical drugs or UV therapy.

### Topical corticosteroids

Throughout this section, the individual studies referred to can be found in Refs [11–13].

### Benefit

**Global estimate of efficacy** The proportion of psoriasis patients with a significant improvement or complete clearance depends on the type, dosage, and duration of use of TC. For topical bethamethasone dipropionate, 46–56% of patients show at least a marked improvement [11,13].

**Different types and dosages of topical corticosteroids** The dosage and treatment duration of TCs depend on the preparation (Class I–IV). Basically, TCs are applied daily at the affected site and after a satisfying response are tapered down. Typically, TCs are applied once daily for 3 weeks after which it is tapered down to once very other day over a period of 1–2 weeks or restricted during three consecutive days a week [10,11,13]. Most of the studies assess TC ointment, but several studies have investigated other galenic forms of TC.

For bethamethasone dipropionate, mometasone furoate or clobetasol 17-propionate, there are no eligible studies directly comparing the efficacy of once versus twice daily [11,13].

**Different topical corticosteroids versus placebo** Treatment success of bethamethasone dipropionate 0.05 mg/g (class III TC) has been demonstrated in almost a dozen trials after 2–6 weeks of use. Two large RCTs by Douglas *et al.* and Papp *et al.* reported significant improvement or complete clearance within 4 weeks in 46% and 56%, respectively, using bethamethasone dipropionate ointment twice daily. In a study by Kaufman *et al.*, 37% of patients treated with topical bethamethasone dipropionate once daily responded successfully. The Cochrane review included studies on bethamethasone dipropionate and showed a mean of  $-1.00$  (95% CI,  $-0.32$ ,  $-1.68$ ), demonstrating a large and significant effect compared with placebo.

Of the four eligible studies on mometasone furoate ointment, which is also a class III TC, one was placebo controlled and showed a good efficacy of this drug in chronic plaque psoriasis [11,13]. A study by Peharda *et al.* showed that once-daily application resulted in 64% of patients in a 75% improvement. Two studies examined the effect of mometasone furoate twice daily showing 50% or more improvement in 68% and 77% of patients [11]. The meta-analysis of the Cochrane review showed a mean of  $-0.75$ , indicating the effect of mometasone furoate is clearly significant.

Eleven studies were included that showed significant efficacy of monotherapy of clobetasol 17-propionate (class IV TC) resulting in a mean of  $-1.24$  (95% CI,  $-0.98$ ,  $-1.50$ ) [11–13]. Nine of the 11 trials applied this drug twice daily. The drug can be administered in different galenics. Twice-daily clobetasol 17-propionate ointment was effective in 89% of patients after 2 weeks. Two studies comparing the efficacy of cream versus lotion showed little difference. For example, Decroix *et al.* reported significant improvement or complete clearance after 4 weeks in 78% (cream), 75% (lotion), and 15% (placebo). Use of a foam preparation was successful in 27% of patients after 2 weeks in one study, but in 68% in another study. Menter *et al.* reported that a clobetasol 17-propionate spray twice daily resulted in a (near) complete clearance in 75% of patients. In summary, ointment appears to be the most effective, and it remains impossible to differentiate between cream, lotion, foam, and spray on the available evidence [11,13].

One small study compared the efficacy of class III versus IV corticosteroids: 89% of patients using clobetasol 17-propionate and 78% of patients using bethamethasone dipropionate had 75% or more improvement. In the Mason *et al.* review [12], class IV corticosteroids were superior to class III steroids.

**Topical corticosteroids versus vitamin D3 analogues** See under calcipotriol.

**Topical corticosteroids in combination therapy** Two studies compared TCs with or without salicylic acid. Katz *et al.* showed that adding 5% salicylic acid to mometasone furoate ointment increased the response rate from 77% to 86% [11,13]. Similarly, bethamethasone dipropionate plus salicylic acid was more effective than bethamethasone dipropionate ointment alone (53% vs 36%) because of enhanced penetration of the TC.

### Harms

The risk of adverse events and their frequency depends on the potency of the TC, site of application, and duration of use [10–13]. Long-term use of a potent TC results in atrophy, but this may be less of a concern in psoriasis than in other skin conditions, and moderate-strength TCs (e.g., triamcinolone acetonide and mometasone) can be tolerated over a longer period of time. Atrophy is a

special concern for continuous use of (very) potent TCs on the face and intertriginous areas and to a lesser extent on the remaining body, and is of relatively little concern on the palms, soles, and scalp. In general, it is recommended to use potent and very potent TCs for no longer than 4 and 8 weeks continuously [10]. Application of TC may increase the risk of superinfection, especially in the intertriginous region. On the face, TC application can provoke steroid acne, rosacea, and perioral dermatitis [10,11,13].

Rare, but possible systemic effects are Cushing syndrome, osteonecrosis, growth retardation, cataracts, glaucoma, and suppression of the hypothalamic–pituitary–adrenal axis [13]. The greatest risk of systemic effects occurs when very potent TCs are used over a large surface for a prolonged period of time and/or are used under occlusion [13]. Of the very potent TCs, less than 50 g per week should be used [13].

The use of TCs has not been associated with birth defects. However, prolonged use of TCs applied over large areas may affect the growth of the fetus and induce adrenal cortex atrophy. TCs are secreted in the breast milk. There are no known drug interactions.

### Comments

TCs remain the cornerstone in the topical treatment of psoriasis. Both class III and IV are very effective in inducing remission, but class IV appears superior. Mild TCs are recommended for psoriasis in the face and intertriginous areas and in infants and children. It remains unclear whether once- or twice-daily is recommended, but the frequency as well as duration should be tapered down in a maintenance phase because long-term use of TCs may lead to cutaneous and systemic adverse effects. Of these side effects, skin atrophy is the most common, but seems less of an issue in patients with psoriasis than in patients with other skin diseases, such as atopic dermatitis. Nevertheless, be aware that continuous use of (very) potent steroids may cause irreversible skin atrophy and striae, cause psoriasis to become unstable, and has systemic effects if used on large surfaces. The ointment vehicle appears most effective, but there are a variety of galenic forms to increase feasibility and treatment adherence if needed without losing too much efficacy [13]. The choice among the different galenics depends on disease severity, localization of psoriasis, patient preference, and costs [10,11,13].

### Coal tar

Throughout this section, the individual studies referred to can be found in Refs [11–13].

### Benefit

**Global estimate of efficacy** There are insufficient data for assessing response rate to monotherapy with coal tar [11].

**Different dosages of coal tar** In the included psoriasis trials, coal tar was applied as an ointment in 5% concentration. The “Goeckermann scheme” is application of coal tar for 1 h or more followed by UVB after removing the tar preparation.

**Coal tar versus placebo** One of six eligible studies compared monotherapy liquor carbonis detergens preparation to base showing basically no difference (48% vs 35% response rate after 4 weeks) [11]. In the pooled analyses, monotherapy of coal tar was not considered superior to placebo (mean,  $-0.48$ ; 95% CI,  $-1.15$ ,  $+0.18$ ) [12].



**Coal tar versus vitamin D3 derivatives** On the basis of two small studies, pooling of data demonstrated that calcipotriol monotherapy was significantly superior to coal tar (mean,  $-1.13$ ; 95% CI,  $-1.60, -0.67$ ) [11,12].

**Coal tar in combination therapy** Coal tar followed by UVB therapy has been studied in six small studies with various designs (UVB frequency, duration of contact, bilateral comparisons) and most frequently including hospitalized patients. This combination therapy seemed effective, but it ranged from 41% to 100% and was not always statistically superior to placebo ointment [11].

A study by Pinheiro *et al.* showed that only 49% of patients had a significant improvement or clearance using a combination of 5% coal tar, 2% allantoin and 0.5% hydrocortisone compared with 72% using calcipotriol monotherapy [11,13].

### Harms

The most common side effect is the brown staining of the skin and clothing and an unpleasant odor. In combination with UV exposure, coal tar can induce solar dermatitis due to photosensitization [11]. Coal tar is carcinogenic in humans (e.g., genital cancer) and various animal models [10–13]. Therefore, coal tar is contraindicated in patients with genodermatoses associated with skin cancer, and a history of skin cancer is a relative contraindication. Coal tar products are contraindicated in pregnant and nursing women.

### Comments

Based on the available literature, coal tar monotherapy is not recommended for the therapy of chronic plaque-type psoriasis. In combination with UV therapy, it may be considered in individual patients in day-care settings or during hospitalization. The uncertainty of its carcinogenic effects during skin therapy, its staining, and odor decrease its acceptance by patients.

### Tazarotene

Throughout this section, the individual studies referred to can be found in Refs [11–13].

### Benefit

**Global estimate of efficacy** About half the patients show 50% improvement using 0.1% tazarotene gel after 12 weeks [11,13].

**Different dosages of tazarotene** Tazarotene gel 0.1% is applied once daily, preferable in the evening, to the affected sites only ( $<10\%$  BSA).

**Tazarotene versus placebo** In the German guideline, seven psoriasis studies assessing tazarotene monotherapy were eligible [11]. Weinstein *et al.* showed that 59% of patients treated with tazarotene 0.1% cream, 48% of those treated with tazarotene 0.05% cream, and 26% of placebo-treated patients had at least an improvement of 50% [11]. The difference between tazarotene 0.1% and 0.05% cream was not statistically different. Gollnick and Menter reported 80% of patients showed a similar improvement using 0.1% tazarotene gel after 12 weeks. However, Green *et al.* reported the same result for only 35% of patients using 0.1% tazarotene gel. In the pooled analyses done by Mason *et al.*, monotherapy of tazarotene was superior to placebo [12].

No studies were included that compared tazarotene with other active topical agents.

**Tazarotene in combination therapy** Green and Sadoff compared various combinations of tazarotene and TCs and best results were achieved with tazarotene plus bethamethasone dipropionate or mometasone cream (78% and 66%, respectively, had 50% improvement) [11,13]. Tazarotene and mometasone ointment in the morning and tazarotene in the evening resulted in a 50% improvement in 83% of patients. Another study suggested an increase in efficacy from 81% to 95% from combining tazarotene with low- to high-potency TCs.

### Harms

Topical tazarotene frequently causes dose-dependent skin irritation, such as itching, burning, and redness. To reduce this tazarotene-induced skin irritation it is often combined with a TC [11,13]. Moreover, tazarotene should not be combined with other topical irritative therapies. Tazarotene may be photosensitizing due to thinning of the epidermis. Long-term use over large areas may result in side effects observed in oral retinoid use [11,13]. Oral tazarotene causes birth defects in mice, and topical application in humans has led to fetal skeletal changes. It is passed on through breast milk.

### Comments

Although tazarotene 0.1% gel once daily can be quite effective in the treatment of localized psoriasis, its use is restricted by the induced skin irritation. To reduce skin irritation, combination therapy with a TC can be indicated.

### Vitamin D analogues

Throughout this section, the individual studies referred to can be found in Refs [11–13].

### Benefit

**Global estimate of efficacy** Between 30 and 50% of patients experience significant improvement or complete clearance after 4–6 weeks use of vitamin D analogues [11,13].

**Different dosages of vitamin D analogues** Calcipotriol and calcitriol can be used once or twice daily in the initial and maintenance phases, whereas tacalcitol is recommended to be used once daily [11]. The maximum of affected skin treated with vitamin D analogues is 30%, 35%, and 20% for calcipotriol, calcitriol, and tacalcitol, respectively [11,13]. Calcipotriol is available in a cream and lotion (no longer in an ointment) and calcitriol and tacalcitol in an ointment.

**Vitamin D analogues versus placebo** The Cochrane review included 15 studies on calcipotriol versus placebo and confirmed a significant effect of calcipotriol with a mean  $-1.02$  (95% CI,  $-0.83, -1.21$ ) [12]. Three large and high-quality studies reported that between 33.4% and 50.7% of patients had a marked improvement and/or were clear after twice-daily application of calcipotriol [11,13]. This response rate further increased up to 74% if duration of use was extended up to 8–12 weeks. Calcipotriol solution was successful in 60% of patients with scalp psoriasis compared with 17% of placebo patients [13]. There are no direct comparative studies of once- versus twice-daily calcipotriol, but once seems less effective than twice daily [11].

In the German guidelines, five studies evaluating calcitriol met the eligibility criteria [11]. Camarasa *et al.* showed a significant improvement or clearance in 52% of patients and Hutchinson in

32% of patients after applying calcitriol twice daily. However, the Cochrane review failed to show that calcitriol was statistically superior to placebo (mean,  $-1.03$ ; 95% CI,  $-2.25, +0.19$ ) [12].

One tacalcitol study showed that 18% and 25% of patients were successfully treated after 4 weeks and 6 weeks, respectively [11,13]. The pooled analysis of three studies suggested that tacalcitol was significantly more effective than placebo (mean,  $-0.82$ ; 95% CI,  $-1.34, -0.29$ ) [12].

**Comparative studies with drug class** A study by Zhu *et al.* showed no significant difference in clinical response between calcipotriol and calcitriol, which was confirmed by the pooled analysis in the Cochrane review [11–13]. On the basis of one large study, calcipotriol appeared more effective than tacalcitol (22% vs 18% of patients achieved a significant response and/or were clear after 4 weeks) [11,13]. The superiority of calcipotriol over tacalcitol was confirmed in the Cochrane review (mean,  $-0.47$ ; 95% CI,  $-0.21, -0.73$ ) [12]. There are no direct comparative studies between calcitriol and tacalcitol.

**Calcipotriol versus tacrolimus** One study by Ortonne *et al.* showed that comparable proportion of patients using calcipotriol and tacrolimus scored “much better” on the PGA after 12 weeks (48.6% vs 44.4%) [11].

**Calcipotriol versus class III steroid** Four studies compared the efficacy of (once or twice) daily calcipotriol and class III steroids showing that the topical steroids were significantly more effective (difference between drugs was between 7.7% and 22.4% in favor of the steroids) [11]. The Cochrane review included nine studies and demonstrated a slight, but not significant, advantage for steroid therapy of 0.19 (95% CI,  $-0.17, +0.55$ ) [12].

**Calcipotriol versus dithranol** Van de Kerkhof *et al.* have shown in two studies that calcipotriol was more significantly effective and had a more rapid response than dithranol cream in the first month [11,13]. However, after 12 weeks the therapeutic success was slightly higher for dithranol compared with calcipotriol (63.8% vs 59.8%). However, a pooled analysis of five studies suggested that dithranol and calcipotriol were equally effective (mean,  $-0.01$ ; 95% CI,  $-0.71, +0.69$ ) [12].

**Vitamin D analogues in combination therapy** In the German guideline, 20 studies were included that assessed the efficacy of vitamin D analogues in combination with topical and/or systemic therapy [11]. The combination can be categorized in topical combination therapy: combination drugs in one preparation (in ointment or gel) and sequential therapy [11]. Twelve studies evaluated the combination therapy of calcitriol and bethamethasone dipropionate once or twice daily. The advantage of this combination is to reduce the skin irritation induced by calcipotriol, and it may have a corticosteroid-sparing effect as well. After 4 weeks of therapy, 45–63.3% of patients responded well to this combination drug once daily [11,13]. Increasing the frequency of application to twice daily increased the efficacy up to 68.0–76.1% of patients in three large and high-quality studies. The Cochrane review confirmed the superiority of twice-daily therapy of calcitriol and bethamethasone dipropionate to once daily (mean, 0.67; 95% CI, 0.36, 0.97). In the first month, the combination drug is more effective than each of the components separately in multiple studies with large numbers of patients. Several studies investigated the maintenance therapy

following a 4-week induction therapy with the combination drug and suggested that continued use of the combination drug is more effective in reducing the mean PASI than calcipotriol monotherapy in the maintenance phase [11]. Two large studies showed that the combination drug in a gel formulation was effective in 68% of patients with scalp psoriasis and was superior to calcipotriol solution ( $<45\%$  in both studies) [11]. Combination therapy with clobetasol and calcipotriol is also superior to calcipotriol monotherapy (mean, 0.60; 95% CI, 0.18, 1.02) [11].

Combination use of calcipotriol with salicylic acid or dithranol may diminish the effectiveness of calcipotriol and is, therefore, not recommended. Tacalcitol combined with UVB therapy was clinically not more effective than UVB monotherapy [11,13]. In combination with cyclosporine (CyA), tacalcitol once daily was more effective than three times weekly, but the 11% difference was not statistically significant [11,13]. It is recommended to not use vitamin D analogues prior to phototherapy because it may reduce the effectiveness of the both therapies.

### Harms

About a quarter of patients report mild discomfort (e.g., burning, pruritus, edema, peeling, dryness, erythema) at site of application, especially in the folds and on the face. Skin irritation is often transitory, may be less common for tacalcitol than for calcipotriol, and can be managed by reducing the dose and/or adding a TC. For the combination drug, the side-effect profile of TC applies. If used properly, the rate of adverse events is extremely low and is on the order of 0.01% [13]. Systemic adverse events such as hypercalcemia and parathyroid hormone suppression are very rare and are associated with an overdose [13]. Therefore, take total BSA that is treated into consideration (the maximum for the different vitamin analogues varies between 20 and 35%; see above) [11]. The rule of thumb is to use less than 100 g of calcipotriol per week [13]. Vitamin D analogues have not been shown to be teratogenic in mice, but should be avoided during pregnancy in humans. It is unclear whether this drug class is excreted in breast milk.

Altogether, there are no absolute contraindications for vitamin D analogues. Relative contraindications are patients with psoriasis pustulosa, disorders of calcium metabolism, those taking drugs affecting calcium metabolism (e.g., thiazide diuretics), severe renal or liver impairment, or during pregnancy and lactation [11,13].

### Comments

Of the vitamin D analogues, calcipotriol and calcitriol are equally modestly effective and superior to tacalcitol. Calcipotriol has been more extensively studied in mono and combination therapy. Combination with topical steroids in a combination drug is significantly superior to calcipotriol monotherapy. Vitamin D analogues may be irritative, but are safe in the long term if the dose remains within limits (e.g.,  $<30\%$  BSA or 100 g weekly for calcipotriol) and is not administered to patients with disorders affecting the calcium metabolism.

## Phototherapy

### How effective are different phototherapies for chronic plaque-type psoriasis?

#### Sources of information

- NICE. Psoriasis: the assessment and management of psoriasis, 2012 [10];

- Nast *et al.* Germa S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11];
- European S3-guidelines on the systemic treatment of psoriasis vulgaris, 2009 [14];
- Koek *et al.*: Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study) [15];
- Menter *et al.*: Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy [16];
- Zweegers *et al.*: Summary of the Dutch S3-guidelines on the treatment of psoriasis 2011, Dermatology Online Journal 2014; 20(3). [17];
- Naldi *et al.*: In *Psoriasis Evidence-Based Dermatology*, 2008 [18].

### Ultraviolet B phototherapy

Besides broadband UVB (BB-UVB) phototherapy (280–315 nm), since the 1980s narrowband UVB (NB-UVB) phototherapy (wavelength around 311 nm) has also been used for treatment of psoriasis. “Selective UV therapy (SUP)” is irradiation with UVB rays with wavelengths between 300 and 320 nm in a unit with rotating base and fitted lamps. Excimer lasers have been used which emit monochromatic UVB light (308 nm).

Often, UVB therapy is combined with topicals, sometimes with systemics [14].

### Benefit

There is a big variation between the studies with UVB in relation to UV dose, number of exposures per week, and treatment duration. Often, time till clearance is mentioned as outcome parameter [11].

**Global estimate of efficacy** Based on RCT evidence, it is shown that with NB- and BB-UVB therapy 50–75% of patients achieve at least a 75 % improvement in PASI score after 4–6 weeks. The number of weeks needed to achieve this level of improvement decreases with the increasing number of exposures per week. There is limited RCT evidence that thrice-weekly UVB cleared psoriasis faster than twice-weekly UVB did. Clearance within 20 weeks was reported in 51%, 63%, and 75% of patients treated twice weekly with NB-UVB. Onset of action starts at 1–2 weeks [11].

Based on a comparison of RCTs of BB-UVB and NB-UVB, there was no statistically significant difference between thrice-weekly selective BB-UVB and thrice-weekly NB-UVB for clearance at the end of treatment, remaining clear at 3 and 6 months post treatment and withdrawal due to toxicity [10].

Excimer laser treatment is investigated in small non-RCTs for solitary psoriatic plaques. Partial remission to complete clearance of skin lesions was achieved in most to all treated patients after an 8-week treatment. A tapering schedule may help to maintain remission. Excimer treatment may be safe in children.

SUP treatment three times per week versus once daily showed a PASI 75 in 29% of patients versus 86% within 4 weeks in this group. One study comparing SUP with BB-UVB showed that SUP was more effective.

**Home ultraviolet B** Patients with psoriasis who are compliant, motivated, and adherent with instructions and follow-up examinations could, under dermatologist supervision, be considered appropriate candidates for home UVB therapy. A recent multicenter,

single-blind, randomized clinical trial of 196 patients from the Netherlands demonstrated that home NB-UVB is just as effective as outpatient-administered NB-UVB. In this study, 70% of patients treated at home compared with 73% treated in the outpatient setting reached PASI 50 [15].

**Ultraviolet B versus psoralen–ultraviolet A** Based on a comparison of RCTs of two- or three-times-weekly oral psoralen–UVA (PUVA) versus two- or three-times-weekly NB-UVB, statistically significantly better results were shown for PUVA in terms of relapse rate for clearers after 6–12 months and mean time to clearance after a maximum follow-up of 3 months.

In terms of PASI 75 at 3–4 months or after a maximum of 20 treatments, there was no statistically significant difference between two- or three-times-weekly NB-UVB and two- or three-times-weekly PUVA [10].

### Ultraviolet B in combination therapy

**Ultraviolet B with emollients** Emollients may increase the transmission of UV radiation by altering the optical properties of psoriatic skin lesions and improving therapeutic efficacy. Emollients such as mineral oil may be applied before UV exposure [16]. There are no RCTs to prove the benefit of concomitant use of emollients with UVB.

**Balneo phototherapy** There seems to be an additive benefit of combining a mineral salt water bath with phototherapy. UVB therapy preceded by mineral salt water bath or high-concentration mineral salt water bath may increase the PASI 75 response. UVB therapy alone led to a PASI 75 response in 50% (or 54%) of patients, and among those who were given a mineral salt water bath (or high-concentration mineral salt water bath) the rates were 73% (or 83%) after 6 weeks of treatment [11].

**Ultraviolet B with vitamin D derivatives** There are conflicting data of the beneficial effect of the combination of vitamin D derivatives plus UVB. Some studies show no superiority above UVB therapy alone [11]. However, RCTs suggest that combining NB-UVB with calcipotriol has a UVB-sparing effect [16].

If applied in combination with UVB therapy, vitamin D derivatives should be applied after UV exposure because some vitamin D analogues may be degraded after exposure to UV radiation. This combination therapy may be potential carcinogenic.

**Ultraviolet B with topical steroids** Response rates of UVB phototherapy in combination with steroids were similar to UVB monotherapy [11]. A synergistic effect is not seen. However, a more rapid clearing of psoriasis occurred when UVB was used in conjunction with topical fluocinolone or clobetasol propionate (used in combination with UVB and topical anthralin). Combined treatment of UV and topical steroids may result in a higher relapse rate. Thus, it is unclear whether the use of topical steroids in combination with UVB is beneficial [16].

**Ultraviolet B with tazarotene** UVB phototherapy may also be combined with tazarotene. In one study, the patients with combination treatment achieved at least 75% improvement in 82% of treated patients after 81 days, compared with 68% in the UVB monotherapy group [11]. The UV dose may need to be adjusted because of higher rates of burning.

**Ultraviolet B with dithranol** One study on the combination of three or five doses of dithranol and broadband UVB phototherapy showed comparable response rates of 40% and 44% (minimum 75% improvement of skin lesion after 8 weeks) for five-times-weekly therapy [11].

The Ingram scheme combines a tar bath, UVB phototherapy and dithranol. One study reported complete clearance of skin lesions in 82% of patients within 20 days.

**Ultraviolet B with coal tar (Goeckerman)** Methodological poor-quality studies are available for the combination of phototherapy and coal tar. Coal tar followed by UVB therapy has been studied in six small studies with various designs (UVB frequency, duration of contact, bilateral comparisons) and most frequently including hospitalized patients. This combination therapy seemed effective, but it ranged from 41% to 100% and was not always statistically superior to placebo ointment [11].

Although Goeckerman and Ingram regimens may be highly effective in clearing psoriasis, these combinations are far less popular in recent years. The treatments are time consuming and messy, and reimbursements for inpatient dermatologic care for psoriasis have been changed [16].

**Ultraviolet B with methotrexate** The combination of methotrexate (MTX) with UVB therapy may be beneficial with the promise of a reduction in dose-related toxicity [16]. There are preliminary indications that MTX could mediate increased phototoxicity of UVB radiation [11].

**Ultraviolet B with cyclosporine** The combination of CyA and UVB has not been studied extensively because of the increased risk of nonmelanoma skin cancer; there are no studies documenting the longer term safety of the combination and it should be avoided [16].

**Ultraviolet B with retinoids** Retinoids combined with UVB have been extensively studied and accelerate the response to phototherapy, reducing the cumulative dosage of UVB and the dose of acitretin required to achieve psoriasis clearance [16].

In an RCT comparing the combination of acitretin with NB-UVB versus acitretin and PUVA therapy, clearance was observed in 57% of patients in the former group compared with 63% in the latter [16].

When phototherapy is combined with acitretin, acitretin should be started approximately 2 weeks before the initiation of phototherapy, the standard dose being 25 mg/day for patients weighing 70 kg or more or 10 mg/day for those weighing less. The dosage and scheduling of BB-UVB or NB-UVB are managed according to the patient's skin type with appropriate reductions (approximately 25%) in the initial dosages of UV radiation. Acitretin has also been used in combination with home NB-UVB phototherapy. Acitretin in combination with UV therapy, despite the reduction of cumulative dosing, costs, and potential systemic toxicities, remains less used than expected given the potential benefits.

**Ultraviolet B with biologics** Only case reports are available to evaluate the effect of combining UVB phototherapy and biologic agents [16]. More research is needed.

## Harms

**Ultraviolet B (broad spectrum, 311 nm; selective ultraviolet therapy, 308 nm)** In general, limited data are available about undesirable

adverse effects of UVB therapy. Erythema is mentioned as a side effect of all UVB modalities, except for excimer laser (308 nm). The frequency of occurrence is unclear. The rate varies between 33% for BB-UVB twice weekly, 73% for NB-UVB and 65% for SUP. Symptoms related to severe dermatitis solaris are more common with excimer laser therapy. Other side effects are blistering, a burning sensation during therapy, as well as areas of brown discoloration and hyperpigmentation [11].

In general, the combination of topical therapies with phototherapy does not increase the rate of adverse effects.

Long-term use of UVB phototherapy results in sun damage and premature aging of the skin. Controversy exists about the potential carcinogenic effects of UVB phototherapy. Animal experiments have demonstrated the carcinogenic effects of UVB phototherapy. These appear to be less pronounced, however, in narrow-spectrum therapy than in broad-spectrum UVB [17]. In a systematic review (search date 2002) limited evidence was found that UVB treatment increases the risk of skin cancer during a follow-up period of around 25 years [18].

The combination of tar and UVB seems not to increase the incidence of nonmelanoma skin cancers over UVB alone [16].

## Comments

UVB is recommended for induction therapy for moderate to severe chronic plaque-type psoriasis in patients that cannot be controlled with topical treatments alone or if there are contraindications for topical therapy or involvement of a large BSA. Treatment with UVB phototherapy can be given two or three times a week [11].

Because of the lower risk of nonmelanoma skin cancer and owing to a better feasibility, UVB is preferred above PUVA, despite the superior efficacy of PUVA compared with UVB therapy alone.

The use of an excimer laser may be recommended for targeted therapy of individual psoriatic plaques.

Given the number of variables involved, there is a wide array of treatment protocols.

Consider topical adjunctive therapy in UVB patients who have recalcitrant plaques to phototherapy alone, or at difficult-to-treat or high-need sites [10]. The customary combination with many topicals may be recommended based on clinical experience, but not on the basis of the available data [11].

The NICE guidelines suggest [10]:

Offer other second- or third-line treatment options when: narrowband UVB phototherapy results in an inadequate response or is poorly tolerated or there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or the person is at especially high risk of skin cancer.

UVB phototherapy is generally considered to be safe during pregnancy (low-quality studies) [17]. UVB phototherapy should not routinely be used as maintenance therapy.

Only trained personnel should give phototherapy. They should be competent in its use, and promote adherence to the indications for and contraindications to treatment, dosimetry, and national policy on safety standards for phototherapy [10].

Patients with a known history of lupus erythematosus or xeroderma pigmentosum should not be treated with phototherapy or photochemotherapy. Patients with a history of a photosensitivity disorder, taking photosensitizing medications, with a history of (familial) melanoma, with atypical nevi, with multiple risk factors



for melanoma, with multiple nonmelanoma skin cancers, or who are immunosuppressed as a result of organ transplantation should be screened carefully before initiating phototherapy or photochemotherapy [16].

Protective goggles should cover the eyes during UV light therapy. Unless psoriasis lesions are present and require UVB therapy, face, neck, backs of the hands, and genital regions should be protected from exposure to UV light.

The entire skin should be inspected for signs of cancerous lesions, precancerous lesions, and dysplastic nevus cell nevi before starting UV treatment. The patient should be informed about the course of therapy, possible side effects, and potential long-term risks – in particular, the increased risk of cancer as a result of therapy. Additional sun exposure should be avoided owing to its synergistic effect. Document the cumulative UV dose, number of UV exposures, and UV sessions [11]. Complete lists of contraindications are described in above-mentioned guidelines.

### Photochemotherapy (psoralen–ultraviolet A)

#### Benefit

Since the 1970s, the administration of photosensitizing psoralens followed by whole-body or partial-body UVA phototherapy (315–400 nm) has been supported by scientific findings. Psoralens may be given systemically, as oral PUVA therapy, or topically as a bath or cream [11].

There is a big variation between studies with PUVA in relation to UV dose, number of exposures per week, and treatment duration. Often, time till clearance is mentioned as an outcome parameter [11].

#### Global estimate of efficacy

**Oral psoralen–ultraviolet A therapy** Most studies used 8-methoxypsoralen 0.6 mg per kilogram of body weight as the photosensitizer. 5-Methoxypsoralen 1.2 mg per kilogram of body weight is also possible but much less investigated. In one comparative study, 8-methoxypsoralen was found to be the superior photosensitizer. The treatment frequency was two to four exposures per week. Based on skin type or minimum phototoxic dosage, the UV dosage was increased.

In the majority of studies, more than 75–100% of patients achieved a score of 75% improvement, even at only two exposures per week. Two studies directly compared increasing the dosage based on skin type versus an MPD-based dosage increase with variable results. Many patients experience remission up to 6 months.

**Bath psoralen–ultraviolet A** There are studies examining the efficacy of bath PUVA, administered in two, three, or four sessions per week. Studies comparing bath PUVA with oral PUVA therapy with a same number of treatments showed equal efficacy. In one study, 64% of patients reported at least a 75% improvement in skin lesions; another showed complete clearance in all patients, which occurred within 10 weeks for twice-weekly therapy or within 4 weeks for four-times-weekly treatment [11].

**Cream psoralen–ultraviolet A** In a study comparing cream (three times per week) with oral PUVA, four-times-weekly use of cream PUVA therapy led to complete clearance in 88% of treated patients, which was lower than in the oral PUVA group [11].

Three studies compared cream PUVA with UVB 311 nm. In one study the effectiveness was the same as with 311 nm therapy [11].

**Psoralen–ultraviolet B** Two studies compared the efficacy of psoralen and UVB with classic oral PUVA therapy. In 6–12 weeks, oral PUVA was shown to be superior (complete clearance in 86% or 84% of oral PUVA patients compared with 77% or 63% of PUVB) [11]. A systematic review included five studies in which no difference was shown [18].

#### Combination therapy

**Psoralen–ultraviolet A with ultraviolet B** Small studies suggest that the combination of PUVA and BB-UVB, NB-UVB, or excimer laser may lead to improved results within shorter periods of time [16]. In one study, the combination of oral PUVA and UVB phototherapy led to complete clearance in all patients within 15–18 sessions. Combined treatment was superior to oral PUVA monotherapy in the comparison group (clearance in 73% of patients within 20 treatments) [11].

The quality of studies with accompanying treatments such as balneotherapy, bath therapy, or climatotherapy is limited [11].

**Psoralen–ultraviolet A with vitamin D3 derivatives** The combination of topical calcipotriol cream or ointment with PUVA leads to a decrease in the duration of PUVA therapy along with an improved clinical response [16]. The combination of calcipotriol with oral PUVA therapy increases its effectiveness (PASI 75 of 87% of combined treated patients in 22 days vs 63% after 34 days in the PUVA group) [11]. For combination use of vitamin D derivatives with PUVA, up to one-fourth of patients experience adverse effects, usually erythema [11].

**Psoralen–ultraviolet A with tazarotene** The combination of PUVA and tazarotene has been anecdotally reported to be synergistic [16].

**Psoralen–ultraviolet A with topical steroids** The combination of betamethasone with oral PUVA may have a synergistic effect. The duration till clearance in the combined group is shorter (average of 13.6 days) compared with oral PUVA (average 20.25 days) [11]. However, it is not clear whether topical steroids combined with oral PUVA is a useful combination: one study found that the combination led to faster clearing without any shortening in the duration of remission, whereas another study found that adding topical steroids results in shorter remissions [16].

**Phototherapy with dithranol** The Ingram scheme combines a tar bath, UV phototherapy, and dithranol. The only study that was included in the guidelines on this treatment method reported complete clearance of skin lesions in 82% of patients within 20 days; in the comparison group, which was given oral PUVA, this same was true for 91% within 34 days.

**PUVA with retinoids** Because of the increased risk for developing cutaneous malignancies with PUVA, PUVA may be administered in combination with other medications such as retinoids or in rotation with other therapies to minimize the total dosage of PUVA [16]. The combination of oral retinoids with PUVA is more effective than monotherapy with either acitretin or PUVA alone. When adding an oral retinoid to a regimen of PUVA therapy, both the number of PUVA treatments and the total amount of UVA exposure are decreased.

In fact, acitretin, when combined with PUVA therapy, is associated with a decreased incidence of squamous cell carcinoma (SCC).

The optimal approach to combination therapy is to initiate treatment with an oral retinoid for approximately 2 weeks before adding PUVA treatment.

Because of their teratogenicity, oral retinoids are contraindicated in women of childbearing potential [16].

*Psoralen-ultraviolet A with cyclosporine* PUVA treatment has an increased risk for developing SCC when subsequently treated with CyA; this combination should be avoided [16].

*Psoralen-ultraviolet A with methotrexate* Although some studies suggest that the combination of PUVA and MTX is more effective than either therapy alone, the safety of this combination has been questioned [14]. The side effects are not yet defined and require long-term study. One potential side effect of combined MTX-PUVA therapy is increased phototoxicity [11].

*Psoralen-ultraviolet A with biologics* No studies evaluating the safety and efficacy of the combination of any biologic agents with PUVA are available [16].

*Narrowband ultraviolet B compared with oral psoralen-ultraviolet A* Based on a comparison of RCTs of two- or three-times-weekly oral PUVA versus two- or three-times-weekly NB-UVB showed statistically significantly better results for PUVA in terms of relapse rate for clearers after 6–12 months and mean time to clearance after a maximum follow-up of 3 months.

In terms of PASI 75 at 3–4 months or after a maximum of 20 treatments, there was no statistically significant difference between two- or three-times weekly NB-UVB and two- or three-times weekly PUVA [10].

One study demonstrated similar rates of clearing with both treatments twice weekly. A double-blind RCT compared NB-UVB with PUVA in 93 patients and demonstrated more patients with complete remission with longer remission times in fewer treatment sessions with oral PUVA [16].

### Harms

In general, limited data are available about undesirable short-term adverse effects of PUVA therapy. Side effects of oral PUVA are erythema, pruritus, and nausea. Most studies report erythema in about 50% (9–80%) of patients. Most other studies reported pruritus in 25–46% (in one study in about 83%). Nausea is the third most commonly reported side effect, affecting around 35% of patients. Dizziness is often reported as a relevant adverse effect, but only one study gave an exact figure of 60% [16].

With bath PUVA, erythema and pruritus are the most common side effects of therapy. Compared with oral PUVA given at the same frequency, the results for these two side effects favor bath PUVA. Nausea did not occur at all. Insufficient data are available on the carcinogenic risk of long-term topical PUVA [11].

Erythema is a rare side effect of cream PUVA (5%). Blistering is also reported [16].

In general, the combination of topical therapies with phototherapy does not increase the rate of adverse effects [16].

### Long-term safety of psoralen-ultraviolet A

The carcinogenic effects of oral PUVA are undisputed. There is an association with an increased risk of developing spinocellular and basal cell cancer, which increases depending on cumulative UVA dose. Although there are reports on an increased risk of melanoma

following long-term therapy, the actual risk is still unclear. In two cohort studies, after a mean follow-up of 14.7 years no increase in the risk of spinocellular carcinoma was found. This suggests that bath PUVA is possibly safer than oral PUVA [18].

Oral PUVA therapy can also lead to disorders of pigmentation, brown spots (PUVA lentigines), and cataracts [17].

### Comments

PUVA is recommended for induction therapy for moderate to severe chronic plaque-type psoriasis, especially if there is involvement of a large BSA. However, NB-UVB therapy may be considered as the first choice for phototherapy. Feasibility is better and there is a lower risk of malignancy. PUVA may be offered to people with plaque psoriasis that cannot be controlled with topical alone or UVB treatments. Treatment with PUVA can be given two or three times a week.

Given the number of variables involved, there is a wide array of treatment protocols [11].

The NICE guidelines mention [10]:

Offer other second- or third-line treatment options when: PUVA results in an inadequate response or is poorly tolerated or there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or the person is at especially high risk of skin cancer.

Consider topical adjunctive therapy in PUVA patients who have recalcitrant plaques to phototherapy alone, or at difficult-to-treat or high-need sites [10]. The customary combination with many topicals may be recommended based on clinical experience, but not on the basis of the available data [11].

Only trained personnel should give phototherapy. They should be competent in its use, and promote adherence to the indications for and contraindications to treatment, dosimetry, and national policy on safety standards for phototherapy [10]. Patients need to be clinically monitored during treatment. Special attention should be paid to the therapeutically desirable level of erythema [11].

Patients with a known history of lupus erythematosus or xeroderma pigmentosum should not be treated with phototherapy or photochemotherapy. Patients with a history of a photosensitivity disorder, taking photosensitizing medications, with a history of (familial) melanoma, with atypical nevi, with multiple risk factors for melanoma, with multiple nonmelanoma skin cancers, or who are immunosuppressed as a result of organ transplantation should be screened carefully before initiating phototherapy or photochemotherapy [16].

Protective goggles should cover the eyes during UV light therapy. Unless psoriasis lesions are present and require PUVA therapy, face, neck, backs of the hands, and genital regions should be protected from exposure to UV light.

The entire skin should be inspected for signs of cancerous lesions, precancerous lesions, and dysplastic nevus cell nevi before starting UV treatment. The patient should be informed about the course of therapy, possible side effects, and potential long-term risks – in particular, the increased risk of cancer as a result of therapy. Additional sun exposure should be avoided owing to its synergistic effect. Document the cumulative UV dose, number of UV exposures, and UV sessions [11].

Ensure that all phototherapy equipment is safety checked and maintained in line with local and national policy [10].

PUVA should not be applied to pregnant and nursing patients and avoided in patients with lighter skin types (Fitzpatrick type I and II), in patients with a personal history of skin cancer, or in people who have already received 150 PUVA treatments or more, and patients who are likely to require CyA or long-term MTX.

Insufficient evidence is available for treating pediatric psoriasis [17]. Do not routinely use PUVA as maintenance therapy. Do not routinely offer co-therapy with acitretin when administering PUVA [10].

Do not use PUVA for pregnant or nursing women. PUVA treatment should be avoided in children, in patients with lighter skin types (Fitzpatrick type I and II), in patients with a personal history of skin cancer, or in people who have already received 150 PUVA treatments or more, patients who are likely to require CyA or long-term MTX.

When considering PUVA for psoriasis, the patient should be informed about the course of therapy, possible side effects, and potential long-term risks – in particular, the increased risk of cancer as a result of therapy. Additional sun exposure should be avoided owing to its possibly synergistic harm. Document the cumulative UV dose, number of UV exposures, and UV sessions [11]. Offer lifetime skin cancer surveillance to people treated with PUVA who have had more than 150–200 PUVA treatments (1000 J/cm<sup>2</sup>) or developed skin cancer [16,17]. Complete lists of contraindications are described in the above-mentioned guidelines.

## Systemic treatment of chronic plaque-type psoriasis

### How effective are systemic treatments for limited stable chronic plaque psoriasis?

#### Acitretin

##### Sources of information

- NICE National Clinical Guideline Centre. Psoriasis, Management of Psoriasis, Clinical Guideline, October 2012 (search date March 8, 2012, Medline, Embase, Cochrane, CINAHL) [10];
- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11].

##### Benefit

**Global estimate of efficacy** With acitretin in a dosage of 40 mg/day a PASI 75 response can be expected in about 23–30% of the patients [11]. The results reported in the trials show a large heterogeneity.

**Acitretin versus placebo** In three trials comparing acitretin versus placebo, varying results were seen with respect to the statistical superiority of its efficacy when compared with placebo [10]. A dose of 50 mg acitretin was significantly better than placebo at week 8 [10], whereas lower dosages (10 and 25 mg) failed to achieve statistical superiority at week 8. In another trial, statistical superiority was not even achieved with a dosage of 75 mg [10].

**Different dosages of acitretin** One study comparing acitretin 50 or 75 mg with 10 mg acitretin showed better improvement with the high dosages with respect to scaling, erythema, thickness, and pustulation at 8 weeks [10]. Another small trial showed better response rates with acitretin 50–75 mg than with acitretin 10–25 mg [11].

**Acitretin versus etanercept** Two trials compared acitretin 0.4 mg per kilogram body weight versus etanercept twice weekly 50 mg and

twice weekly 25 mg. In both trials, response rates were better for etanercept than for acitretin [11].

**Acitretin in combination with etanercept** One trial looked at a treatment with etanercept 25 mg twice weekly versus acitretin 0.4 mg per kilogram body weight daily versus the combination of once-weekly etanercept 25 mg with acitretin 0.4 mg per kilogram body weight daily. After 24 weeks, both etanercept groups showed statistically significant better results than acitretin alone [11].

**Acitretin in combination with ultraviolet therapy** See section on phototherapy.

##### Harms

Most people experience mucocutaneous adverse effects, such as dry skin, cheilitis, and conjunctivitis. Mucocutaneous effects are generally mild. Increased serum cholesterol and triglyceride concentrations occurred in about half of the people. Occasionally, acute hepatitis occurred, possibly as an idiosyncratic hypersensitivity reaction. Radiographic evidence of extraspinal tendon and ligament calcifications has been documented. In a small number of patients, acitretin is transformed into etretinate. This is additionally promoted by alcohol consumption. Etretinate accumulates in the body fat and can cause a long-term safety risk, especially in women of childbearing age.

##### Comments

The efficacy of acitretin as a monotherapy in low dosages is rather small; the use of higher dosages is usually accompanied by an increase in adverse drug reactions. Giving acitretin to women of childbearing age should be avoided. If it is given to women of childbearing age, effective contraception must be given for 1 month before starting acitretin, throughout the treatment, and for 2 years after stopping acitretin treatment. Acitretin may be considered for special cases such as patients with HIV or a prior history of malignancies.

##### Fumaric acid esters

The preparation contains a mixture of dimethyl fumarate and three salts of ethyl hydrogen fumarate. Dimethyl fumarate is considered to be the actual active ingredient. Fumaric acid derivatives are widely used in Germany but are not licensed in other European countries or in the USA.

##### Sources of information

- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11];
- Griffiths *et al.*: A systematic review of treatments for severe psoriasis [19].

##### Benefit

**Global estimate of efficacy** With fumaric acid derivatives a PASI 75 response can be expected in about 50–70% of the patients after 16 weeks [11].

**Fumaric acid esters versus placebo** Two of the RCTs (123 people) compared a mixture of dimethylfumaric and monoethylfumaric acid esters versus placebo. Pooled analysis found that this mixture of fumaric acid derivatives reduced severity significantly more than placebo at 16 weeks. The remaining RCTs published in a single

paper documented that the response to dimethylfumaric acid ester was significantly greater than placebo at 16 weeks, whereas the response to monoethylfumaric acid ester was no greater than to placebo [19].

### Harms

All of the RCTs had high withdrawal rates. Acute adverse effects, including flushing and gastrointestinal symptoms, were reported in up to 75% of the patients. Additional adverse effects include diarrhea, stomach cramps, flushing, and lymphocytopenia [19].

### Comments

Fumaric acid esters show better efficacy than placebo. The clinical experience in some countries with fumaric acid esters, in particular in Germany, is much greater than the documentation of efficacy and safety of their use in clinical studies. In Germany, they are widely used for long-term therapy and are considered a very safe treatment. Clinical use of the drug is limited by gastrointestinal effects and flushing.

### Methotrexate

#### Sources of information

- NICE National Clinical Guideline Centre. Psoriasis, Management of Psoriasis, Clinical Guideline, October 2012 (search date March 8, 2012, Medline, Embase, Cochrane, CINAHL) [10];
- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11].

### Benefit

**Global estimate of efficacy** With MTX a PASI 75 response can be expected in about 25–50% of the patients [11].

**Methotrexate versus placebo** Two trials compare MTX versus placebo. MTX was statistically better than placebo for PASI 50 and PASI 75 at 4–6 months [10].

**Methotrexate versus cyclosporine** Four trials compared CyA with MTX. The studies identified do not show a clear superiority of one over the other. For some study outcomes CyA was better than MTX (e.g., PASI 75 after 12 weeks), for others MTX was better than CyA (e.g., final PASI at week 12) [10]. The time till the onset of action is faster with CyA than with MTX [10].

### Harms

The most common symptomatic adverse effect of MTX therapy is nausea, which may affect up to one-third of treated patients. Its most important potential side effect is acute myelosuppression, which is the cause of most of the rare deaths attributable to it when used as a therapy for psoriasis [20]. MTX is eliminated largely via the kidneys, and toxic levels may build up rapidly in the presence of renal impairment. Particular care is required in the elderly, in whom renal function may deteriorate rapidly in response to acute illness; dietary folate deficiency may add to the toxicity. Some studies have shown that circulating homocysteine levels are elevated in psoriasis patients receiving MTX, but that folate supplementation can reverse this abnormality; since raised homocysteine levels have been associated with atherothrombotic vascular disease, it may therefore be advisable for all patients on MTX to receive folate supplementation [21]. Certain drugs, particularly nonsteroidal anti-inflammatory agents, aspirin, trimethoprim, and sulfona-

mides, may interfere with MTX pharmacokinetics and thus increase the risk of toxicity, particularly in the presence of impaired renal function. Long-term MTX treatment carries with it a risk of hepatic fibrosis and cirrhosis, which is considered to increase with cumulative dose. In general, patients with diabetes, obesity, and relevant alcohol consumption are considered to be at a higher risk of hepatotoxicity. However, and probably mostly due to too small and not well-designed studies, it has not been possible to clearly define possible risk groups or the relevance of a cumulative dose of more than 3 g in the respective studies [10].

Safety monitoring for MTX remains a challenge. Current guidelines suggest using standard liver function tests and serial serum procollagen III levels for monitoring [10,11]. Pulmonary disease associated with MTX has been described as an acute or chronic interstitial pneumonitis [22]. MTX appears to double the risk of developing SCC in patients exposed to psoralen plus UVA and may be an independent risk factor for this type of cancer in patients with psoriatic arthritis [23]. A higher risk of lymphoproliferative diseases in long-term users has been suggested by a few case reports. On the basis of data from a large case series (248 patients), the cumulative incidence of lymphoma is not expected to be much higher than 1% [24].

### Comments

In most countries MTX is the most frequently prescribed systemic treatment. It is considered to be particularly valuable for patients with concomitant arthritis. The clinical experience with MTX is much greater than the documentation of its efficacy and safety in clinical studies. Recently published trials have yielded lower efficacy data than earlier trials, and the data must be interpreted with caution; different initial dosages may influence early study assessments. For some patients it seems to be a very suitable and safe long-term treatment. Patients using MTX should be closely monitored for liver toxicity and should be advised to limit their alcohol consumption.

### Cyclosporine

#### Sources of information

- NICE National Clinical Guideline Centre. Psoriasis, Management of Psoriasis, Clinical Guideline, October 2012 (search date March 8, 2012, Medline, Embase, Cochrane, CINAHL) [10];
- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11];
- Griffiths *et al.*: A systematic review of treatments for severe psoriasis [19].

### Benefit

**Global estimate of efficacy** With CyA a PASI 75 response can be expected in about 50–75% of the patients after 12–16 weeks [11].

**Cyclosporine versus placebo for clearance** Four RCTs compare CyA versus placebo. In most trials, CyA was significantly better than placebo [25–28].

**Cyclosporine versus placebo for maintenance** Five RCTs looked at a treatment with CyA to maintain remission. Two RCTs compared two doses of CyA (1.5 mg/kg or 3.0 mg/kg daily) versus placebo. Both RCTs found that 3.0 mg/kg daily CyA was better than placebo for maintaining remission. The third RCT compared two different CyA formulations and found no significant difference in the



response after 24 weeks between an oil-based and microemulsion preconcentrate formulation. The fourth RCT (400 patients) found that tapering the CyA dose marginally increased the time to relapse in comparison with abrupt stopping of CyA (time to relapse 113 days with tapered CyA versus 109 days with abrupt stopping;  $P = 0.038$ ). The fifth RCT (37 patients) found that, over the 36 months of treatment, continuous CyA was more effective for maintaining remission than intermittent CyA (remission maintained for 69% of the observation period with continuous CyA versus 32% with intermittent treatment) [19].

*Cyclosporine versus methotrexate* See section on methotrexate.

### Harms

CyA can be associated with dose-related increases in hypertension and reduced renal function [19]. Observational evidence suggests that the incidence of these adverse events increases over time. In a case-series follow-up study of 122 consecutive patients treated continuously with CyA for 3–76 months at dosages not exceeding 5 mg/kg daily, 104 patients discontinued treatment [29]. The mean percentage of patients who discontinued treatment due to adverse effects (mostly renal dysfunction and hypertension) rose from 14% at 12 months to 41% at 48 months. One prospective cohort study documented an increased risk of malignancies in 152 people with psoriasis treated with CyA for up to 5 years. Malignancies were diagnosed in 3.8% of patients, with a standardized incidence ratio of 2.1 in comparison with the general population. There was a sixfold increase in the incidence of skin cancer in comparison with the general population, while non-skin malignancies did not show a significantly increased risk [30]. The additional use of UV, especially PUVA, strongly increases the risk of nonmelanoma skin cancer.

### Comments

CyA is an established short-term treatment option for moderate to severe psoriasis. Relapses are often seen on withdrawal, and long-term treatment is limited by adverse effects (mainly renal dysfunction and hypertension).

### Adalimumab

#### Sources of information

- NICE National Clinical Guideline Centre. Psoriasis, Management of Psoriasis, Clinical Guideline, October 2012 (search date March 8, 2012, Medline, Embase, Cochrane, CINAHL) [10];
- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11], tables updated searching for “adalimumab” and “psoriasis” using RCT filter on Medline on September 15, 2012;
- Singh *et al.*: Adverse effects of biologics: a network meta-analysis and Cochrane overview [31].

### Benefit

*Global estimate of efficacy* With adalimumab a PASI 75 response ranging between 71 and 80% can be expected after 16 weeks [11].

*Adalimumab versus placebo* See Table 26.1 (modified and updated from [11]).

*Adalimumab for patients with or without prior exposure to biological therapy* Three studies assessed the likeliness of a treatment success if the patient has had prior exposure to biological therapy. In the

studies included, there was no statistically significant difference with respect to a PASI 75 response at week 16 or at week 24 if the patient had prior biologic treatment or not [10].

### Harms (based on German S3 guidelines [11])

Injection site reactions were the most commonly reported adverse effect. In placebo-controlled studies they were seen with adalimumab in 20% of the patients and in 14% of placebo-treated patients). Adalimumab therapy can be associated with an increased rate of infections, particularly infections of the upper respiratory passages, bronchitis, and infections of the urinary passages. Severe infections such as pneumonia, septic arthritis, post-operative infections, erysipelas, phlegmonous infections, diverticulitis, and pyelonephritis can also occur.

Less frequently observed adverse events include thrombocytopenia and leukopenia, exanthema, urticaria, angioedema, pruritus, respiratory distress, as well as tightness in the chest.

Induction of auto-antibodies (ANA, anti-dsDNA antibodies) and lupus-like syndrome has been reported in rare cases. A Cochrane review by Singh *et al.* from 2011 summarizes the safety data from several biologics, including adalimumab [31]. It is important to note that this analysis also includes other patient groups among psoriasis patients, such as those with rheumatoid arthritis and patients with Crohn's disease. With adalimumab compared with placebo there was neither a significant increase in the OR for the “total number of adverse events,” the “number of withdrawals due to adverse events,” nor in “serious infections or serious adverse events.”

### Comments

Adalimumab shows good efficacy in the treatment of psoriasis vulgaris. With a large number of patients having been treated with adalimumab also in other indications, the risk–benefit profile appears to be good.

### Etanercept

#### Sources of information

- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11], tables updated searching for “etanercept” and “psoriasis” using RCT filter on Medline on September 15, 2012;
- Singh *et al.*: Adverse effects of biologics: a network meta-analysis and Cochrane overview [31].

### Benefit

*Global estimate of efficacy* With etanercept  $2 \times 25$  mg or  $1 \times 50$  mg weekly about 35% or 38% of patients achieve PASI 75 after 12 weeks. During a therapy with  $2 \times 50$  mg every week for 12 weeks, about 50% of patients achieve a PASI 75 response [11].

*Etanercept versus placebo* The study results of the major trials are provided in Table 26.2 (adapted from [11]).

### Harms (based on German S3 guidelines [11])

Placebo-controlled studies report injection site reactions in 14% of psoriasis patients treated with etanercept (11–17%) compared with 7% in the placebo group [32]. An elevated risk of serious infection or malignancies has to be considered, especially with respect to lymphoma. As with other tumor necrosis factor (TNF)-blockers, undesirable hematological effects, demyelinating diseases, and autoimmune processes may occur.

Table 26.1 Adalimumab.

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Gordon [40]	2006	Adalimumab 80mg (w0) + 40mg EOW (from w1) SC	46	10	w12	PASI 50: 76% PASI 75: 53% (24/45) PASI 100: 11%	w24	PASI 100: 13%	w1–12: 28 (62.2%) w12–60: 72 (78.3%) (arm 1 and 3)	w1–12: 1 (2%) w12–60: 2 (2.2%) (arm 1 and 3)	—	2 ×	till w12 +
						PASI 50: 88% PASI 75: 80% (40/50) PASI 100: 26%		PASI 100: 24%	w1–12: 39 (78%) w12–60: 39 (78%)	w1–12: 4 (8.0%) w12–60: 7 (14.0%)			
						PASI 75: 4% (2/52) PASI 100: 0%		PASI 100: 11%	w1–12: 35 (67.3%)	w1–12: 0			
Menter [41]	2008	Adalimumab 80mg at w0, adalimumab 40mg at w1, then adalimumab EOW SC till w33, then responders randomized to adalimumab 40mg EOW or placebo EOW till w52	814	w12: 31	w12	PASI 75: 68% PASI 90: 37% PASI 100: 14%	w16	PASI 75: 71% (578/814) PASI 90: 45% PASI 100: 20%	w16: 1155	w16: 17	—	2 ×	+
						PASI 75: 5% PASI 90: 2% PASI 100: <1%		PASI 75: 7% (26/398) PASI 90: 2% PASI 100: 1%	w16: 498	w16: 7			
						PASI 50: 26.4% PASI 75: 15.1% PASI 90: 7.5%		PASI 50: 30.2% PASI 75: 18.9% PASI 100: 11.3%	Pts: 42 (79.2%)	1 (1.9%)	Data not consistent in publications		
Revicki [42] + Saurat [43]	2008	Adalimumab 80mg (w0) + 40mg EOW	108	4	w12	PASI 50: 90.7% PASI 75: 76.9% PASI 100: 48.1%	w16	PASI 50: 88% PASI 75: 79.6% PASI 100: 51.3%	Pts: 79 (73.8%)	2 (1.9%)		2 ×	+
						PASI 50: 54.5% PASI 75: 24.5% PASI 100: 9.1%		PASI 50: 61.8% PASI 75: 35.5% PASI 100: 13.6%	Pts: 89 (80.9%)	1 (0.9%)			
						PASI 75: 2.2% PASI 900: 0%		PASI 50: 19.6% PASI 75: 4.3% PASI 90: 0%	41 (89.1%)	2 (4.3%)	Starting at w16 top. corticosteroids for non-responders (placebo: 30 [65.2%], adalimumab: 8 [6.5%])		
Asahina [44]	2010	Placebo	46	6	w12	PASI 75: 2.2% PASI 900: 0%	w16	PASI 50: 19.6% PASI 75: 4.3% PASI 90: 0%	41 (89.1%)	2 (4.3%)	Starting at w16 top. corticosteroids for non-responders (placebo: 30 [65.2%], adalimumab: 8 [6.5%])	2 ×	+
						PASI 75: 44.7% PASI 90: 21.1%		PASI 50: 81.4% PASI 75: 62.8% PASI 90: 39.5%	39 (90.7%)	3 (7.0%)			
						PASI 75: 53.5% PASI 90: 30.2%		PASI 50: 73.7% PASI 75: 57.9% PASI 90: 36.8%	37 (97.4%)	0			
		Adalimumab 80mg EOW	42	4	w12	PASI 75: 73.8% PASI 90: 45.2%	w16	PASI 50: 90.5% PASI 75: 81.0% PASI 90: 61.9%	38 (90.5%)	1 (2.4%)		2 ×	+

AE, adverse event; BW, twice weekly; BW, body weight; EOW, every other week; ITT, intention to treat; mITT, modified ITT; ni, not indicated; pts, patients; QD, once per day; QW, once per week; SAE, serious adverse event; tR, total remission; w, week.

Table 26.2 Etanercept.

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Gottlieb [45]	2003	Placebo	55	43	w12	PASI 50: 11% PASI 75: 2% (1/55) PASI 90: 0%	w24	PASI 50: 13% PASI 75: 5% (3/55) PASI 90: 0%	ni	3	—	2 ×	+
Leonardi [32]	2003	Placebo	166	43	w12	PASI 50: 14% (24/166) PASI 75: 4% (6/166) PASI 90: 1% (1/166)	w24	ni	ni	ni	After 12w, pts in the placebo group began twice-weekly treatment with 25 mg of etanercept	2 ×	—
Papp [46]	2005	Etanercept 25 mg SC	196	11	w12	PASI 50: 64% (126/196) PASI 75: 34% (67/196) PASI 90: 11% (21/196)	w16	PASI 75: 35%* PASI 90: 77% (127/164)	ni	11	* Data out of graph, sensitivity analyses	3 ×	+
Papp [46]	2005	Etanercept 50 mg SC w0–12, etanercept 25 mg BIW SC w13–24	194	9	w12	PASI 50: 77% (150/194) PASI 75: 49% (96/194) PASI 90: 21% (41/194)	w16	PASI 75: 46%*	ni	1			
Papp [46]	2005	Placebo	193	25	w12	PASI 50: 9% (18/193) PASI 75: 3% (6/193) PASI 90: 1% (1/193)	w16	PASI 75: 9%*	ni	1			

Continued

Table 26.2 Continued

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Tyring [47]	2006	Etanercept 50mg BIW SC	311	6	w12	PASI 50: 74% (230/311) PASI 75: 47% (147/311) PASI 90: 21% (65/311)	—	—	at least 1 AE: 153 (49.0%)	9 pts (11 SAEs)	—	3 ×	+
		Placebo w0–12, etanercept 50mg BIW (w13–96)	309	15		PASI 50: 14% (43/306) PASI 75: 5% (15/306) PASI 90: 1% (3/306)			at least 1 AE: 137 (44.8%)				
Cassano [48]	2006	Etanercept 50mg (BIW)	53	3	w12	PASI 50: 74% PASI 75: 54%	—	—	ni	ni	—	1 ×	LOCF
		Etanercept 100mg 1 ×/w	55	4		PASI 50: 78% PASI 75: 50%							
Moore [49]	2007	Etanercept 50mg BIW w0–12, etanercept 50mg QW w13–24	1272	155	w12	PGA clear or almost clear: 46.9%	w16	PGA clear or almost clear: 45.2%	688 pts (54.1%)	40 pts (3.1%)	—	—	+
		Etanercept 50mg BIW w0–12, reinjection at w16 or w20	1274	190		PGA clear or almost clear: 47.6%		PGA clear or almost clear: 27.6%	671 pts (52.7%)	39 pts (3.1%)			
Gisondi [50]	2008	Etanercept 25mg BIW SC	22	0	w12	PASI 50: 40% PASI 75: 20%	w18	PASI 50: 53% PASI 75: 36%	0	0	Data out of graph	1 ×	+
		Etanercept 25mg/w + Acitretin 0.4mg/kg BW QD	18			PASI 50: 37% PASI 75: 15%		PASI 50: 48% PASI 75: 33%	1				
		Acitretin 0.4 mg/kg BW QD	20	4		PASI 50: 22% PASI 75: 8%		PASI 50: 33% PASI 75: 12%	2				
Van de Kerkhof [51]	2008	Placebo w0–12, etanercept 50mg QW w13–24	46	10	w12	PASI 50: 8.7% (4/46) PASI 75: 2.2% (1/46) PASI 90: 2.2% (1/46)	w16	PASI 50: 38% PASI 75: 18% PASI 90: 4%	ni	6.5% in first 12w	* Data out of graph	2 ×	+
		Etanercept 50mg w0–24	96	6		PASI 50: 68.8% (66/96) PASI 75: 37.5% (36/96) PASI 90: 13.5% (13/96)		PASI 50: 81% PASI 75: 55% PASI 90: 23%		2.1% in first 12w			
Caproni [52]	2009	Etanercept 2 × 50mg/w	30	0	w12	PASI 50: 86.7% (26/30) PASI 75: 56.7% (17/30)	—	—	ni	ni	—	—	—
		Acitretin 0.4 mg/kg per day	30			PASI 50: 66.7% (20/30) PASI 75: 26.7% (8/30)							



Cassano [53]	2010	Etanercept 50 mg BIW w0-12	36	3	w12	PASI 50: 33 (92%) PASI 75: 19 (53%)	w24	PASI 50: 33 PASI 75: 29	ni	ni	—	—	ni
		Etanercept 50 mg QW (responders: 50 mg QW w12-36)	36			PASI 50: 27 (75%) PASI 75: 13 (36%)		PASI 50: 27 PASI 75: 19					
Prinz [54]	2011	Etanercept 50 mg BIW w1-12, etanercept 50 mg QW w13-24	379	29 (7.7%)	w12	PASI 75: 54.9% (207/377)	w24	PASI 75: 70.3% (265/377)	14 (3.7%)	ni	—	2 ×	mITT
		Etanercept 50 mg QW w1-24	373	28 (7.5%)		PASI 75: 36.4% (135/371)		PASI 75: 62.3% (231/371)	10 (2.7%)				
Berends [55]	2007	Etanercept 50 mg BIW w 1-12, etanercept 25 mg BIW w 13-24	28	w12: 1	w12	PASI 50: 39% (11/28) PASI 75: 82% (23/28)	—	—	23 (82%)	ni	—	—	ITT
		Etanercept 25 mg BIW w1-24	17	w12: 2		PASI 50: 24% (4/17) PASI 75: 71% (12/17)			17 (100%)				
		Efalizumab 0.7 mg/kg BW first dosage, then 1 mg/kg BW QW w1-24	17	w12: 5		PASI 50: 6% (1/17) PASI 75: 59% (10/17)			14 (82%)				
Strober [56]	2011	Brokinumab 200 mg w0+4, then brokinumab 100 mg at w8	139	8	w12	PASI 75: 80.6% PASI 90: 55.4% PASI 100: 28.8%	—	—	50.40%	2 (1.4%)	—	2 ×	ITT
		Etanercept 50 mg BIW for 12w	139	12		PASI 75: 39.6% PASI 90: 13.7% PASI 100: 5.8%			49.60%	1 (0.7%)			
		Placebo for 12w	72	6		PASI 75: 6.9% PASI 90: 4.2% PASI 100: 0%			44.40%	2 (2.8%)			
Gottlieb [57]	2011	Brokinumab 200 mg w0+4, then brokinumab 100 mg at w8	138	10	w12	PASI 75: 81% PASI 90: 60% PASI 100: 38%			68 (49.3%)	4 (2.9%)	Data out of graph	2 ×	ITT
		Etanercept 50 mg BIW for 12w	141	7		PASI 75: 57% PASI 90: 22% PASI 100: 8%			76 (53.9%)	1 (0.7%)			
		Placebo for 12w	68	5		PASI 75: 9% PASI 90: 1% PASI 100: 0%			31 (45.6%)	1 (1.5%)			

AE, adverse event; BIW, twice weekly; BW, body weight; EOW, every other week; ITT, intention to treat; mITT, modified ITT; ni, not indicated; pts, patients; QD, once per day; QW, once per week; SAE, serious adverse event; tR, total remission; w, week.

A Cochrane review by Singh *et al.* from 2011 summarizes the safety data from several biologics, including etanercept [31]. It is important to note that this analysis also includes other patient groups among psoriasis patients, such as those with rheumatoid arthritis and patients with Crohn's disease. With etanercept, when compared with placebo, there was neither a significant increase in the OR for the "total number of adverse events," the "number of withdrawals due to adverse events," nor in "serious infections or serious adverse events."

### Comments

Etanercept shows moderate efficacy in the treatment of plaque-type psoriasis during induction therapy. The dosage of once-weekly 50 mg or twice-weekly 50 mg should be preferred over twice-weekly 25 mg. With a large number of patients also having been treated with etanercept in other indications, the risk-benefit profile appears to be good.

## Infliximab

### Sources of information

- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11], tables updated searching for "infliximab" and "psoriasis" using RCT filter on Medline on September 15, 2012;
- Singh *et al.*: Adverse effects of biologics: a network meta-analysis and Cochrane overview [31].

### Benefit

**Global estimate of efficacy** With infliximab, 75–88% of the patients achieve a PASI 75 response after 16 weeks [11].

**Infliximab versus placebo** The study results of the major trials are presented in Table 26.3 (adapted from [11]).

### Harms (based on German S3 guidelines [11])

The most commonly reported adverse effects of infliximab are infusion reactions. Usually these reactions are mild, but the probability of an infusion reaction is increased in patients with infliximab-specific antibodies and may include severe reactions such as anaphylactoid reactions. In addition, infliximab therapy has been associated with serious infections. The use of infliximab carries a risk of reactivation and generalization of preexisting latent tuberculosis or other preexisting infections. Infliximab has been associated with exacerbation of existing cardiac insufficiency.

Demyelinating diseases of the central nervous system have been observed, and multiple sclerosis may be exacerbated. Especially in patients with preexisting liver damage (e.g., hepatitis), hepatotoxicity has been observed. In psoriasis patients, elevated transaminase levels have been reported. Leukopenia, neutropenia, thrombopenia, pancytopenia, and related deaths have been reported in patients who have rheumatoid arthritis or Crohn's disease and were taking infliximab. The number of cases of lymphoma in patients treated with anti-TNF- $\alpha$  antibodies is reportedly minimally higher than in control groups. The risk of other malignancies is no greater than the risk reported for controls. It is unclear whether exposure to infliximab could increase the incidence of these diseases. Some patients who take infliximab develop antinuclear antibodies in serum and some also develop dsDNA-antibodies. The reversible onset of lupus erythematosus-like syndrome is occasionally reported.

A Cochrane review by Singh *et al.* from 2011 summarizes the safety data from several biologics, including infliximab [31]. It is important to note that this analysis also includes other patient groups among psoriasis patients, such as those with rheumatoid arthritis and patients with Crohn's disease. With infliximab, the OR for an increase in the "total number of adverse events" and "withdrawals due to adverse events" compared with placebo were significantly increased (OR, 1.55; 95% CI, 1.01–2.359; and OR, 2.34; 95% CI, 1.4–4.14). No statistical significant increase in "serious infections" or "serious adverse events" was seen for infliximab when compared with placebo.

### Comments

Infliximab shows the best efficacy and fastest onset of action in the treatment of psoriasis vulgaris during induction therapy. The very good efficacy has to be counterbalanced with the somewhat increased risk of side effects compared with the other TNF- $\alpha$  antagonists.

## Ustekinumab

### Sources of information

- S3 – Guidelines for the treatment of psoriasis vulgaris: update 2011 (search date November 2009, Medline, Embase, Cochrane) [11], tables updated searching for "ustekinumab" and "psoriasis" using RCT filter on Medline on September 15, 2012;
- Ryan *et al.*: Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials [33];
- Tzellos *et al.*: Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials [34].

### Benefit

**Global estimate of efficacy** With ustekinumab, 67% of the patients can be expected to achieve a PASI 75 response after 16 weeks [11].

**Ustekinumab versus placebo** The study results of the major trials are presented in Table 26.4 (adapted from [11]).

### Harms (based on German S3 guidelines [11])

Ustekinumab is the newest systemic antipsoriatic drug available and the available safety data are limited if compared with the other systemic treatments. In two major trials, PHOENIX-1 and PHOENIX-2, the rate of common and serious side effects related to ustekinumab was comparable to that of placebo. The most common side effects in the two trials were: infections (general), 21.5% and 31.4% (placebo, 20% and 26.7%); specifically nasopharyngitis, 6.8% and 10.2% (placebo, 7.1% and 8.6%); upper respiratory infections, 2.9% and 7.1% (placebo, 3.4% and 6.3%); headache, 4.6% and 5.5% (placebo, 2.4% and 4.1%); and arthralgia, 2.4% and 3.4% (placebo, 2.7% and 2.9%). The rates of serious adverse events in the two trials were 0.8% and 2.0%, and thus within the same ranges as in the placebo group (0.8% and 2.0%). The rate of severe infections was low (<1%) in subsequent phases of the study as well. In both studies together there were 15 malignancies, including 11 cases of skin cancer, during the total observation period. There is ongoing discussion regarding possible major adverse cardiovascular events with the use of ustekinumab. Depending on the statistical approaches taken, meta-analyses of published data came to differing conclusion regarding this association. More data are necessary

Table 26.3 Infliximab.

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Antoni [58]	2005	Placebo w1–21, following infliximab 5 mg/kg every 8w	52	7	w16	PASI 50: 0 PASI 75: 0 PASI 90: 0	—	—	Phase I: 33 pts (65%) Phase II: 44 pts (88%)	Phase I: 1 pt. (2%) Phase II: 6 pts (12%)	* Pts with active psoriasis arthritis	2 ×	+
		Infliximab 5 mg/kg w0/2/6/14, following placebo in w16+18, starting at w22 infliximab 5 mg/kg every 8w	52	10		PASI 50: 100% (22/22) PASI 75: 68% (15/22) PASI 90: 36% (8/22)			Phase I: 38 pts (73%) Phase II: 41 pts (84%)	Phase I: 1 pt. (2%) Phase II: 8 pts (16%)			
Gottlieb [59]	2004	Placebo	51	37	w14	PASI 75: 8%	w18	PASI 75: 9%	32 pts (62.7%)	0	Data out of graph	2 ×	ni
		Infliximab 3 mg/kg w0/2/6	99	30		PASI 75: 59%		PASI 75: 40%	76 pts (77.6%)	4 (4.1%)			
		Infliximab 5 mg/kg w0/2/6	99	18		PASI 75: 87%		PASI 75: 75%	78 pts (78.8%)	8 (8.1%)			
Reich [60]	2005	Infliximab 5 mg/kg IV w0/2/6, then every 8w	301	32 (w24) 30 (w50)	w10	PASI 50: 91% (274/301) PASI 75: 80% (242/301) PASI 90: 57% (172/301)	w24	PASI 50: 90% (248/276) PASI 75: 82% (227/276) PASI 90: 58% (161/276)	82% pts	17 pts (6%)	Data not consistent in publication	3 ×	+
		Placebo w0–24, then infliximab 5 mg/kg IV w24–48	77	9 (w24) 7 (w50)		PASI 50: 8% (6/77) PASI 75: 3% (2/77) PASI 90: 1% (1/77)		PASI 50: 6% (6/77) PASI 75: 4% (3/77) PASI 90: 1% (1/77)	71% pts	2 pts (3%)			

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Table 26.3 Continued

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Menter [61]	2007	Placebo in w0/2/6, then infliximab 5 mg/kg at w16/18/22, then EOW	208	25 (w14) 34 (w50)	w10	PASI 75: 1.9% PASI 90: 0.5%	w26	ni	116 pts (56.0%) till w14	W14: 5 pts (2.4%)	—	2 ×	+
		Infliximab 3 mg/kg BW w0/2/6/14, then re-randomization: every 8w or as needed	313	19 (w14) 91 (w50)		PASI 75: 70.3% PASI 90: 37.1%		PASI 50: 120 (85.1%) PASI 75: 91 (64.5%) PASI 90: 47 (33.3%)	196 pts (62.6%) till w14	W14: 3 pts (1.0%)			
		Infliximab 5 mg/kg BW w0/2/6/14, then re-randomization: every 8w or as needed	314	15 (w14) 71 (w50)		PASI 75: 75.5% PASI 90: 45.2%		PASI 50: 126 (89.4%) PASI 75: 110 (78.0%) PASI 90: 79 (56.0%)	216 pts (68.8%) till w14	W14: 9 pts (2.9%)			
Torii [62]	2010	Placebo switched into infliximab group at w16	19	7	w10	PASI 50: 11%* PASI 75: 0% PASI 90: 0%	w14	PASI 50: 13%* PASI 75: 13%* PASI 90: 7%*	29 AEs in 14 pts (73.7%) till w14	1 serious infection till w14	Data not consistent in publication * Data out of graph	2 ×	+
		Infliximab 5 mg/kg w0/2/6, then every 8w till w62	35	7		PASI 50: 82%* PASI 75: 69%* PASI 90: 54.3%		PASI 50: 85%* PASI 75: 73%* PASI 90: 50%*	93 AEs in 34 pts (97.1%) till w14	1 serious infusion reaction till w14			
Chaudhari [63]	2001	Placebo	11	1	w10	PAS 75: 18% (2/11) PASI-Reduction: 20.3 → 17.5	—	—	14 AEs	0	—	2 ×	—
		Infliximab 5 mg/kg BW w0/2/6	11	1		PASI 75: 82% (9/11) PASI-Reduction: 22.1 → 3.8		—	12 AEs				
		Infliximab 10 mg/kg BW w0/2/6	11	1		PASI 75: 73% (8/11) PASI-Reduction: 26.6 → 5.9		—	19 AEs				
Barker [64]	2011	Infliximab 5 mg/kg BW w0/2/6/14/22	653	112	w16	PASI 75: 78% (508/653)	—	—	80 (12%)	6% (36/649)	Pts with < 50% improvement were allowed to switch groups	—	+
		MTX 15 mg QW (if necessary dose increase to 20 mg at w6)	215	88		PASI 75: 42% (90/215)		—	8 (4%)	2% (4/211)			

AE, adverse event; BW, twice weekly; BW, body weight; EOW, every other week; ITT, intention to treat; mITT, modified ITT; ni, not indicated; pts, patients; QD, once per day; QW, once per week; SAE, serious adverse event; IR, total remission; w, week



Table 26.4 Ustekinumab.

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Leonardi [65]	2008	Placebo w0–12, then ustekinumab 45 mg	255	w12: 12	w12	PASI 50: 10.2% (26/255) PASI 75: 3.1% (8/255) PASI 90: 2% (5/255) PASI 100: 0%	w28	PASI 50: 95.9% (118/123) PASI 75: 65.9% (81/123) PASI 90: 44.7% (55/123) PASI 100: 19.5% (24/123)	123 pts with 1 or more AEs (48.2%) till w12	w12: 2 (0.8%)	—	3 ×	+
						PASI 50: 85.9% (220/256) PASI 75: 66.4% (170/256) PASI 90: 36.7% (94/256) PASI 100: 10.9% (28/256)		PASI 50: 96.3% (234/243) PASI 75: 78.6% (191/243) PASI 90: 55.6% (135/243) PASI 100: 29.2% (71/243)					
						PASI 50: 83.5% (213/255) PASI 75: 67.1% (171/255) PASI 90: 41.6% (106/255) PASI 100: 12.5% (32/255)		PASI 50: 91.2% (228/250) PASI 75: 71.2% (178/250) PASI 90: 49.2% (123/250) PASI 100: 20.8% (51/250)					
						PASI 50: 10.0% (41/410) PASI 75: 3.7% (15/410) PASI 90: 0.7% (3/410) PASI 100: 0%		PASI 50: 93.3% (180/193) PASI 75: 69.9% (135/193) PASI 90: 42.5% (82/193) PASI 100: 15.5% (30/193)					
Papp [66]	2008	Placebo w0–12, then ustekinumab 45 mg	410	w12: 18	w12	PASI 50: 89.3% (367/411) PASI 75: 75.7% (311/411) PASI 90: 50.9% (209/411) PASI 100: 18.2% (75/411)	w28	PASI 50: 95.0% (380/400) PASI 75: 78.5% (314/400) PASI 90: 54.3% (217/400) PASI 100: 29.5% (118/400)	197 pts with 1 or more AEs (47.9%) till w12	w12: 5 (1.2%)	—	3 ×	+
						PASI 50: 83.6% (342/409) PASI 75: 66.7% (273/409) PASI 90: 42.3% (173/409) PASI 100: 18.1% (74/409)		PASI 50: 92.9% (369/397) PASI 75: 69.5% (276/397) PASI 90: 44.8% (178/397) PASI 100: 18.6% (74/397)					
						PASI 50: 10.0% (41/410) PASI 75: 3.7% (15/410) PASI 90: 0.7% (3/410) PASI 100: 0%		PASI 50: 93.3% (180/193) PASI 75: 69.9% (135/193) PASI 90: 42.5% (82/193) PASI 100: 15.5% (30/193)					
						PASI 50: 89.3% (367/411) PASI 75: 75.7% (311/411) PASI 90: 50.9% (209/411) PASI 100: 18.2% (75/411)		PASI 50: 95.0% (380/400) PASI 75: 78.5% (314/400) PASI 90: 54.3% (217/400) PASI 100: 29.5% (118/400)					
Gottlieb [67]	2009	Ustekinumab 90 mg or 63 mg w0–3, placebo in w12+16	76	w12: 6	w12	PASI 75: 52% (33/63) PASI 90: 33% (21/61)	—	—	W12: 46 (61%)	w12: 0	* Pts with psoriasis arthritis	2 ×	+
						PASI 75: 5% (3/55) PASI 90: 4% (2/55)		—					

Continued

Table 26.4 Continued

First author	Year	Drug	No. (n) randomized	No. withdrawals with $\geq 1$ dose of active treatment	Weeks after baseline	Results	Weeks after baseline	Results	Total no. AEs	Total no. SAEs	Comments	Blinding	ITT
Griffiths [68]	2010	Etanercept 50 mg BIW w1–12, then 90 mg for 12w	347	11	w12	PASI 75: 197 (56.8%) PASI 90: 80 (23.1%)	—	—	243 pts with 1 or more AEs (70.0%) till w12	w12: 4 (1.2%)	—	2 ×	+
		Ustekinumab 45 mg w0+4	209	8		PASI 75: 141 (67.5%) PASI 90: 76 (36.4%)			138 pts with 1 or more AEs (66.0%) till w12	w12: 4 (1.9%)			
		Ustekinumab 90 mg w0+4	347	5		PASI 75: 256 (73.8%) PASI 90: 155 (44.7%)			240 pts with 1 or more AEs (69.2%) till w12	w12: 4 (1.2%)			
Tsai [69]	2011	Ustekinumab 45 mg w0/4/16 (placebo at w12)	61	w12: 5	w12	PASI 75: 67.2%	—	—	40 pts with 1 or more AEs (65.6%) till w12	w12: 0	Taiwanese and Korean pts	2 ×	ni
		Placebo w0+4, ustekinumab 45 mg w12+16	60	w12: 4		PASI 75: 5%			42 pts with 1 or more AEs (70%) till w12	w12: 2 (3.3%)			
Igarashi [70]	2012	Ustekinumab 45 mg SC w0+4, then every 12w	64	w12: 4	w12	PASI 50: 82.8% (53/64) PASI 75: 59.4% (38/64) PASI 90: 32.8% (21/64)	—	—	42 pts with 1 or more AEs (65.6%) till w12	w12: 0	Japanese pts. * 1 pt. did not receive active treatment	2 ×	ni
		Ustekinumab 90 mg SC w0+4, then every 12w	62	w12: 0		PASI 50: 83.9% (52/62) PASI 75: 67.7% (42/62) PASI 90: 43.5% (27/62)			37 pts with 1 or more AEs (59.7%) till w12	w12: 3 (4.8%)			
		Placebo at w0+4, then crossover to ustekinumab 45 mg or 90 mg SC at w12/16/28/40/52	32*	w12: 4		PASI 50: 12.9% (4/31) PASI 75: 6.5% (2/31) PASI 90: 3.2% (1/31)			21 pts with 1 or more AEs (65.6%) till w12	w12: 2 (6.3%)			

AE, adverse event; BIW, twice weekly; BW, body weight; EOW, every other week; ITT, intention to treat; mITT, modified ITT; ni, not indicated; pts, patients; QD, once per day; QW, once per week; SAE, serious adverse event; TR, total remission; w, week.

for a final assessment, and special attention has to be given to cardiovascular risk factors before initiating and during a treatment with ustekinumab.

### Comments

Ustekinumab shows good efficacy and a fast onset of action in the treatment of psoriasis vulgaris during induction therapy. Since ustekinumab has been used for a limited number of patients, special attention has to be paid to safety aspects.

### Alefacept

Alefacept is a recombinant protein that binds to the CD2 receptor on memory effector T lymphocytes. With alefacept, a PASI 75 response can be expected in about 21% of the patients [11]. Alefacept is approved for the treatment of psoriasis in the USA and Switzerland only, and its distribution has currently been ceased.

## How effective are treatments for guttate psoriasis?

### Sources of information

- Chalmers *et al.*: Interventions for guttate psoriasis [35];
- Owen *et al.*: Antistreptococcal interventions for guttate and chronic plaque psoriasis [36].

Both reviews were updated using the same search terms in the databases Medline, Embase, and Cochrane (search data August 16, 2012).

## Antistreptococcal interventions

### Benefits

**Antibiotic therapy** The Cochrane review included only one RCT examining the use of antistreptococcal interventions and found no evidence of benefit in any patient receiving either of two antibiotic regimens [36]. Our literature update identified two additional trials investigating the usefulness of antistreptococcal interventions. In one trial, antipsoriatic treatment in both groups was done using betamethasone dipropionate 0.05% cream and UVB. The additional benefit of adding penicillin in one group was assessed and no relevant difference could be seen [37]. The study has to be considered largely underpowered to detect any difference. Another trial randomized 43 psoriasis patients to a treatment with erythromycin, with phenoxymethylpenicillin, or no treatment. Additional antipsoriatic treatments were not applied. No statistically significant improvements were seen in any group [38].

**Tonsillectomy** One trial examining the effects of tonsillectomy on the recurrence or persistence of guttate psoriasis was found. Twenty-nine patients with chronic psoriasis and history of exacerbation after sore throat were randomly assigned to tonsillectomy ( $n = 15$ ) or control ( $n = 14$ ) groups and monitored for 2 years. The mean PASI score decreased significantly in the treatment group, both with time after tonsillectomy and compared with the controls. Eighty-six percent of the controls used topical treatment at some time point during the study, compared with only 27% in the treatment group. Methodological limitations apply since, after tonsillectomy treatments, regimens were not clearly defined. Antipsoriatic treatments were given as considered necessary by the physicians and/or patients and there was no individual reporting on the antipsoriatic treatments given (change in PASI with respect to treatment given) [39].

### Harms

There is insufficient information. Tonsillectomy carries with it a risk of a serious adverse outcome, especially post-operative bleeding.

### Comments

There is no available evidence that the use of antibiotics improves guttate psoriasis. Larger trials with a longer follow-up may be necessary to yield relevant findings. There are indications that patients with chronic psoriasis and a history of exacerbation after sore throat may benefit from tonsillectomy.

## How effective are systemic treatments for acropustulosis (acrodermatitis continua of Hallopeau)?

An additional de novo search was run for the term “acrodermatitis continua of Hallopeau” using Medline (search date August 16, 2011).

We found no RCTs on treatments for acrodermatitis continua of Hallopeau. Only case reports were identified. Several case reports claim good efficacy of adalimumab, etanercept, and infliximab on acrodermatitis continua of Hallopeau. Publications on the success of topical treatments are also available and report on the efficacy of betamethasone, calcipotriol, and tacrolimus, usually applied as combination therapy. Some case reports claim efficacy also for “targeted” UVB therapy or topical 8-methoxypsoralen with UVB. Case reports published before the era of the biologics also report successful treatments with CyA, acitretin, MTX, and dapsone, which are likely to be still used with success, but with a loss of interest in these drugs these are not reported as case reports anymore.

### Key points

The main limitation of the available evidence is the lack of trials comparing different therapeutic options.

### Chronic plaque psoriasis

- There is sufficient evidence to show the efficacy of MTX, CyA, fumaric acid esters, adalimumab, etanercept, infliximab, and ustekinumab. The data on the efficacy of acitretin is limited and varies with respect to the dosage.
- There is good evidence of a risk of serious harm from the major treatment modalities used for treating severe psoriasis, including skin cancer with PUVA and heliotherapy, hypertension and renal impairment with CyA, myelosuppression and hepatic fibrosis with MTX, and teratogenicity with systemic retinoids.
- The safety data for the biologic treatments is increasing but has still to be interpreted with caution, especially with respect the newest treatment ustekinumab.

### Guttate psoriasis

- There is virtually no guidance from controlled trials on how to manage guttate psoriasis.

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# Lichen planus

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## Background

### Definition

Lichen planus (LP) is a chronic inflammatory disease affecting mainly the oral mucosa and the skin. Cutaneous LP is typically a pruritic eruption of shiny, violaceous, flat, polygonal papules, mainly localized on the front of the wrists, the lumbar region, and around the ankles. The most frequent oral presentation is asymptomatic reticular LP, but painful erosive or ulcerative areas may appear. LP may also involve the genitals, esophagus, conjunctiva, nails, and scalp [1].

### Prevalence

The prevalence in the general population of cutaneous LP is 0.1% among women and 0.3% among men, and the prevalence of oral LP is 2.3% among women and 1.5% among men [2,3]. The oral mucosa is the most frequently affected site [1].

### Etiology

The pathogenesis of LP remains unclear. There is some evidence that CD8+ T lymphocytes infiltrating the epidermis and dermis act as effector agents against keratinocytes, but the target antigens are unknown [4].

### Prognosis

Spontaneous remission of cutaneous LP treated with various treatment regimens after 1 year occurs in two-thirds of cases [5]. Patients mainly complain of pruritus and residual pigmentation. Oral LP is a chronic disease and usually does not resolve spontaneously [6]. Erosive LP can be extremely painful, and the most severe form can lead to weight loss. A 1% incidence of squamous-cell carcinoma has been reported among patients with oral LP; however, the true risk remains controversial [7]. Nail or scalp involvement may result in irreversible scars, and genital, esophageal, and conjunctival strictures and fibrosis [1].

### Diagnostic tests

LP histopathology consists of a dermoepidermal papule with hyperkeratosis, hypergranulosis, and acanthosis, basal cell vacuoli-

zation, and a band-like inflammatory infiltrate in the superficial dermis.

### Treatment

The aim of treatment depends on the clinical form, severity, and therapeutic response of LP. For cutaneous LP, the aim of treatment is to reduce pruritus and time to resolution, without inducing severe side effects. Asymptomatic oral LP does not usually require treatment. Symptomatic oral LP may need aggressive treatment to stop pain and obtain a remission. The aim of treating nail, scalp, or erosive genital LP is to stop the inflammatory process as soon as possible to avoid scarring.

### Relevant outcomes

Relevant outcomes in cutaneous LP include patient-reported pruritus intensity and clearance of cutaneous lesions assessed by both clinicians and patients. For oral LP, relevant outcomes are quality of life, patient-reported pain, and evaluation through a validated measure assessed by physicians. In oral LP, the rate of recurrence is high after withdrawal of treatment. The recurrence rate and the tolerance of long-term treatment should be considered. These relevant outcomes were mostly not evaluated in the studies reviewed, which commonly used global evaluation scores [8,9].

### Methods of search

We searched the following databases: Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews in the Cochrane Library until August 8, 2012, using the key words "lichen planus".

## Questions

### Do corticosteroids improve cutaneous lichen planus?

#### Efficacy

One randomized controlled study (RCT) compared the efficacy of oral prednisolone, 30 mg/day, and placebo administered for 10 days in 38 patients [10]. Ten out of 38 patients did not complete

the study; repartition per group, reasons and number of analyzed patients were not described. The median time for LP to clear was 18 weeks in the prednisolone group and 29 weeks in the placebo group ( $P = 0.02$ ). Pruritus at 6 weeks was reported as not statistically different in the two groups. Two patients in the corticosteroids group experienced a severe relapse after treatment withdrawal.

One randomized, unblinded study compared the efficacy of calcipotriol ointment and betamethasone valerate ointment applied twice daily in 31 patients. No differences were observed between the treatments [11]. The side effects of oral prednisolone were minimal [10].

### Implications for practice

Short courses of systemic corticosteroids are usually recommended as first-line treatment for moderate to severe cutaneous LP, although this is not based on relevant clinical trials and recurrences are possible after treatment withdrawal. Topical corticosteroids are recommended as first-line treatment in mild to moderate cutaneous LP. Topical calcipotriol is not recommended.

Although they are widely used, the evidence for corticosteroid efficacy is scant. The poor quality of reporting and the high rate of withdrawn patients in the systemic corticosteroids trial, the absence of blind evaluation, and small size of the calcipotriol trial do not allow any conclusions to be drawn regarding the efficacy of these treatments.

### Do retinoids improve cutaneous lichen planus?

#### Efficacy

We found one RCT evaluating the efficacy of oral retinoids in cutaneous LP [12]: acitretin 30 mg/day versus placebo for 8 weeks in 65 patients. Of the patients in the acitretin group, 64% (18 of 28) improved significantly or had remissions, versus 13% in the placebo group. Tolerability was considered to be good or very good in 73% of the patients [12]. Side effects noted in this study were mainly cheilitis and dry mouth. The most severe side effect of retinoids is teratogenicity.

### Implications for practice

In the relevant RCT neither the duration of the disease before inclusion nor the extent of the lesions were detailed. The criteria for remission and marked improvement were not defined. Furthermore, visible adverse effects of retinoids could have compromised the blinding evaluation [12]. The level of evidence of acitretin efficacy is therefore of average quality.

Because of potential side effects, acitretin is recommended as a second-line treatment for cutaneous LP. Acitretin may also be combined with psoralen-ultraviolet A (PUVA) therapy (see photochemotherapy section that follows).

### Does photochemotherapy improve cutaneous lichen planus?

#### Efficacy

We found a small controlled trial in which 10 patients with cutaneous LP were treated with PUVA therapy on one side of the body [13]. Five out of 10 patients cleared completely on both sides (complete clearance on the first treated side of the body was expected before treating the other side). Patients had a complete response on one side within a mean of 6 weeks.

We did not find RCTs assessing the efficacy of UVB phototherapy. In the largest retrospective, observational study involving 50

patients, 70% of treated patients with narrowband ultraviolet B (UVB) had a complete response within a mean of 11 weeks [14].

No adverse effects were described in the PUVA or UVB trials. Little risk of photoaging or skin cancer exists if the treatment is limited to one or two cycles. This treatment could increase the risk of residual hyperpigmentation in dark-skinned patients.

### Implications for practice

In view of the high rate of spontaneous remission, the evidence for the efficacy of PUVA and UVB TL-01 therapy is weak. Combined treatment with retinoids and PUVA is occasionally recommended, but the efficacy has not been evaluated.

PUVA therapy and UVB TL-01 could be an alternative to oral corticosteroids in moderate to severe cutaneous LP.

### Does griseofulvin, hydroxychloroquine, or sulfasalazine treatment improve cutaneous lichen planus?

#### Efficacy

Two RCTs ( $n = 38$ ,  $n = 48$ ) compared griseofulvin 500 mg/day versus placebo [15,16] and one ( $n = 80$ ) versus hydroxychloroquine 400 mg/day [17]. One RCT compared sulfasalazine maximum 2.5 g/day with placebo [18].

The two trials comparing griseofulvin with placebo and the one comparing griseofulvin with hydroxychloroquine did not report adverse effects. No severe adverse effect was observed in the sulfasalazine trial; however, this treatment has on occasion been associated with life-threatening adverse reactions such as Stevens-Johnson syndrome and pancytopenia.

### Implication for practice

Because of the important discrepancy between trials for cure rate varying between 5 and 80%, unclear risk of bias of the trials, and phototoxic potential, griseofulvin is not recommended for treatment of cutaneous LP. Because of the potential life-threatening adverse reaction, sulfasalazine is not recommended for treatment of cutaneous LP.

### Does methotrexate improve cutaneous lichen planus?

#### Efficacy

There is no RCT assessing the efficacy of methotrexate in LP. We found one retrospective ( $n = 11$ ) [19] and one prospective series ( $n = 24$ ) [20]. Methotrexate was given orally 15–20 mg/week. A complete response was obtained in 10/11 patients after a median of 9.6 weeks of treatment and a cumulative dose of 65–260 mg in the first series [19]. In the prospective series, a complete remission was observed in 14/24 patients at 24 weeks with a cumulative dose of 210–360 mg [19]. In the retrospective series, the only clinical or biological adverse effect observed was nausea and fatigue in one patient, leading to methotrexate withdrawal [19]. In the prospective series, adverse effects were observed in 12 patients (50%): reduced appetite, decrease in hemoglobin, and liver function abnormalities. One patient withdrew [20].

### Implication for practice

Methotrexate by analogy with other cutaneous disease could be used as third-line treatment of generalized LP in case of failure or contraindication to systemic corticosteroids, retinoids, and phototherapy. In the absence of a comparator in a disease known for spontaneous relapse, a spontaneous remission cannot be excluded.

## Do topical corticosteroids improve oral lichen planus?

### Efficacy

#### *Fluocinonide*

We found one RCT [21], in which fluocinonide in an adhesive base, applied six times per day, was compared with its vehicle in 40 patients with oral LP. At 9 weeks the difference significantly favored treatment.

#### *Betamethasone valerate*

One RCT [22] compared betamethasone valerate aerosol, four sprays per day, with placebo in 23 patients with oral LP. At 2 months, eight of 11 patients had a “good or moderate” response in comparison with two moderate responses in the placebo group.

In the two RCTs, the only adverse effect observed was a case of oral candidiasis.

### Implication for practice

Two studies including patients with oral LP of varying degrees of severity provide a low level of evidence for the efficacy of topical corticosteroids in oral LP.

One conclusion of the recently updated Cochrane review on symptomatic oral LP is: “we identified no RCTs that compared steroids with placebo in patients with symptomatic OLP. From the trials in this review there is no evidence that one steroid is any more effective than another” [9]. Despite the absence of evidence, topical corticosteroids are the first-line treatment for oral LP based on clinical practice.

## Do systemic corticosteroids improve oral lichen planus?

### Efficacy

One RCT compared the efficacy of topical triamcinolone with oral betamethasone (5 mg/day for 3 months, followed by a slow taper during 3 months) [23]. No difference for number of patients with improvement of signs and symptoms was observed between the two groups.

Seven patients in the group treated with oral prednisone developed cushingoid features, and one developed diabetes mellitus. Five of patients treated locally developed oral candidiasis [23]. The risk of detection bias considering that outcomes were subjective is high for this unblinded RCT [23].

### Implication for practice

Although systemic corticosteroids are widely used in oral LP, their efficacy has not been documented. Based on clinical practice, systemic corticosteroids 0.5–1 mg/kg are recommended as second-line treatment for erosive oral LP in the absence of response to topical corticosteroid treatment and as first-line treatment in severe oral LP.

## Do retinoids improve oral lichen planus?

### Efficacy

#### *Topical retinoic acid*

We found one RCT ( $n = 20$ ) comparing 0.1% retinoic acid lotion twice daily with placebo in patients with plaque-like LP [24]. After 4 months of therapy, 97% of patients in the tretinoin group had improvement or were cured, in comparison with 21% in the placebo group. An RCT compared 0.05% retinoic acid with fluocinolone acetonide 0.1%, four applications per day [25]. At week 4, clinical

score improvement was significantly greater for the fluocinolone acetonide group.

#### *Isotretinoin gel*

One RCT compared isotretinoin gel twice daily with excipient alone for 2 months in 20 patients [26]. The improvement in scores was 90% and 10%, respectively.

#### *Tazarotene*

One RCT compared tazarotene gel 0.1% versus placebo in 12 patients with hyperkeratotic oral LP. The clinical score was significantly improved in the treatment group [27].

Only mild local side effects were observed.

### Implications for practice

These RCTs included asymptomatic patients, were at high risk of bias, and included a small number of patients. The concentration of 0.05% used in the only trial comparing topical retinoids with topical corticosteroids is lower than the retinoids concentration usually used (0.1%).

Despite the low level of evidence and mainly based on clinical experience, topical retinoid can be recommended as first-line treatment alone or in association with topical corticosteroids for papular-plaque-like form without ulceration oral LP.

## Do topical calcineurin inhibitors improve oral lichen planus?

### Efficacy

#### *Topical ciclosporin*

We found 2 RCTs comparing the efficacy of topical application of ciclosporin with placebo in 16 and 20 patients, respectively [28,29].

There is a statistically significant difference for reducing pain and clinical signs favoring ciclosporin in these two trials.

#### *Tacrolimus*

We don't find a RCT comparing tacrolimus to placebo.

#### *Pimecrolimus*

Three RCTs comparing pimecrolimus cream 1% applied twice daily during 4 weeks [30,31] and 30 days [32] in 12 [31] and 20 [30,32] patients respectively to placebo were selected for inclusion in the two recent Cochrane reviews [8,9].

No difference for pain reduction or clinical outcomes was observed in these three trials except for the physician global assessment in one trial [31]. A forth-trial comparing pimecrolimus to placebo was not included in the Cochrane review [9], because it was not stated that all patients were symptomatic at baseline. There was no comparison between groups in this trial, only difference between end and baseline outcome in each group [33].

The only side effect reported with topical calcineurin inhibitors was a local burning sensation. No elevated serum levels were observed. Current FDA labeling states that topical pimecrolimus and tacrolimus should not be given to treat premalignant conditions.

### Implications for practice

Considering that the two trials are small and possess a high risk of bias, the evidence of efficacy of topical ciclosporin is low [9]. There is no evidence of superiority of pimecrolimus over placebo for treatment of erosive oral LP.



A recent Cochrane review states: "There is weak and unreliable evidence that ciclosporin may reduce pain and clinical signs of OLP. There is no evidence that other calcineurin inhibitors reduce pain compared to either steroids or placebo." [9]

Topical ciclosporin, tacrolimus or pimecrolimus are not recommended for the treatment of oral LP.

### **Are calcineurin inhibitors more effective than topical corticosteroids for treating oral lichen planus?**

#### **Efficacy**

##### **Topical ciclosporin**

Three RCTs compared topical ciclosporin, with topical triamcinolone 0.1%. No difference for pain evaluation or rate of clinical improvement was observed in these trials [34–36]. An RCT compared ciclosporin 1.5% and clobetasol propionate ointment 0.025% [37]. Clobetasol was more effective than ciclosporin in inducing clinical improvement (95% vs 65% of the patients). No difference was observed for pain reduction.

##### **Pimecrolimus**

A RCT comparing pimecrolimus cream 1% to triamcinolone acetate paste 0.1% found no difference between the two treatments [38].

##### **Tacrolimus**

Two trials compared tacrolimus ointment 0.1% with clobetasol propionate 0.5% [39,40]. One found a statistically significant difference favoring tacrolimus for pain and clinical score [39], while no difference between treatments was observed in the other [40]. One trial compared tacrolimus ointment 0.1% with triamcinolone acetate paste 0.1%. The rate of healed and improved patients was not different between groups [41].

#### **Implication for practice**

There are no reliable results demonstrating that topical calcineurin inhibitors are more effective than topical corticosteroids in oral LP.

Topical corticosteroids remain the first-line treatment of symptomatic oral LP.

### **Does topical *Aloe vera* improve oral lichen planus?**

#### **Efficacy**

We found two RCTs ( $n = 54$  [42] and  $n = 64$  [43]) comparing topical *Aloe vera* with placebo. Treatment was applied twice daily for 8 weeks and three times daily for 12 weeks, respectively. One RCT [42] found a statistically significant amelioration at the end of the treatment in the *Aloe vera* group for pain and clinical outcome, while another RCT found no difference [43]. A pooled estimate for the mean clinical score was relative risk 1.34 (95% confidence interval, 1.10–1.62) [9].

An RCT comparing *Aloe vera* gel with triamcinolone acetate paste 0.1% applied four times a day during 4 weeks found no difference between the groups [44].

In these three RCTs, neither symptoms nor erosions were required for inclusion, and no severe adverse effects were reported. The *Aloe vera* preparations used were not standardized and only partially described in terms of component [44] (type of *Aloe vera* extract, excipients) and concentration. There is no data on safety for long-term use of topical *Aloe vera* on erosive mucous membranes [44–46].

#### **Implication for practice**

There is weak evidence that *Aloe vera* may reduce the pain of oral LP and improve the clinical signs of disease compared with placebo [9]. Knowledge on safety is lacking. *Aloe vera* is not recommended for oral LP.

### **Does extracorporeal photochemotherapy improve oral lichen planus?**

#### **Efficacy**

We found two prospective series of seven [47] and 12 [48] patients with resistant severe erosive LP for a mean of 6 years [47] and 7.5 years [47], respectively, who were treated with extracorporeal photochemotherapy, two sessions per week. Complete remission was obtained in all patients in one series [47] and nine out of 12 [48] patients in the other after a mean of 24 [47] and 21 [48] sessions, respectively.

A progressive decrease in blood lymphocytes was observed in all patients, but without significant consequences. In one series, treatment was discontinued in one patient because of difficult venous access [47].

An RCT will probably not be carried out in this severe and rare form of the disease. Well-conducted prospective series currently provide the best level of evidence for this therapy.

#### **Implications for practice**

Because of its cost and availability only in a limited number of centers, extracorporeal photochemotherapy should be restricted to severe erosive LP resistant to other treatments. No comparative studies have yet been conducted.

### **Does other treatment improve oral lichen planus?**

#### **Efficacy**

Several new treatments were compared, each one in a single RCT against placebo (curcuminoids [49], hyaluronic acid [50], ignatia [51], purslane [52], lycopene orally [53]) or corticosteroids (intralesional injection of polysaccharide nucleic acid fraction of bacillus Calmette-Guérin or triamcinolone acetate intralesional injections [54], and thalidomide paste versus dexamethasone paste [55]).

Except for lycopene and purslane, no difference was found between any of these treatments and placebo or corticosteroids. Trials assessing efficacy of etanercept (NCT 00568581) and topical rapamycin (NCT 01061853) are ongoing.

No conclusion can be drawn from these trials owing to unclear or high risk of bias [9].

#### **Implication for practice**

None of these treatments are recommended in treatment of oral LP.

### **Does corticosteroids improve genital, nails or scalp lichen planus?**

#### **Efficacy**

There is no RCT assessing the efficacy of treatments in these LP variants.

We found a prospective cohort study of women with erosive vulvar LP. In 71% of patients symptoms were attenuated with 0.05% clobetasol propionate ointment twice daily without complete resolution [56].

For nails LP, we found two retrospective case series [57,58]. Two-thirds of 142 patients treated with intramuscular injection or oral systemic glucocorticoids and/or intralesional injection or topical glucocorticoids during 6 months were cured or had a major improvement. We did not find a large prospective study for lichen

**Table 27.1** Main treatments for cutaneous and oral lichen planus.

Intervention	Recommendations	Formulation and use
<i>Cutaneous lichen planus</i>		
Topical corticosteroids	First-line treatment for limited cutaneous LP	Very potent corticosteroids (clobetasol propionate ointment 0.05%), at night once daily in thickened lesion of cutaneous LP until remission then maintenance therapy  Potent topical corticosteroids can be used in less severe form of LP or during maintenance therapy
Oral corticosteroids	First-line therapy for widespread cutaneous LP	Prednisolone 0.5–1 mg/kg per day until improvement.
Systemic retinoids	Second-line treatment in cutaneous LP	Acitretin 30 mg/day 8 weeks
Phototherapy	Second-line treatment in cutaneous LP	PUVA, or UVB 2–3 times a week, 12 times alone or associated with systemic retinoids
<i>Oral lichen planus</i>		
Topical corticosteroids	First line treatment for symptomatic oral LP	Very potent corticosteroids (clobetasol propionate ointment 0.05%), 3 times daily until remission and then maintenance therapy  Potent topical corticosteroids can be used in less severe form of LP or during maintenance therapy  Soluble prednisolone tablets, 5 mg in 15 mL water for mouthwash 3 times daily for widespread oral LP
Topical retinoids	Second-line therapy for oral LP in papular and plaque-like white forms and in absence of erosive lesions	Retinoic acid or isotretinoin lotion/ gel 0.1%, twice daily
Oral corticosteroids	First-line therapy for severe erosive LP  Second-line therapy for oral resistant to topical corticosteroids	Prednisolone 0.5–1 mg/kg per day until improvement
Systemic immunosuppressive agents	In patients with cortico-dependent or cortico-resistant erosive LP	E.g., azathioprine, mycophenolate mofetil, methotrexate

Source: Le Cleach and Chosidow, 2012 [1]. Reproduced with permission of Massachusetts Medical Society.

planopilaris. Topical glucocorticoids, either alone or combined with an intralesional glucocorticoid injection, are considered, mainly based on small series and clinical experience, as the first-line treatment for lichen planopilaris [59,60].

**Summary**

Many drugs and physical treatments have been used in the treatment of LP, but there is a lack of well-designed and large trials. Two recent Cochrane systematic reviews found weak evidence or an absence of evidence to support the efficacy of a specific treatment. This statement included evidence for topical or systemic corticosteroids which are currently considered first-line treatment of LP (Table 27.1).

**Key points**

- LP is a chronic inflammatory disease mainly affecting the skin and oral mucosae. The aims of treatment vary depending on the clinical LP variant. There is a lack of well-designed and large trials comparing the usually recommended treatments with placebo.
- We found no evidence for the efficacy of systemic or topical corticosteroids, although this treatment is usually recommended as the first-line treatment for cutaneous LP.
- We found limited evidence of the efficacy of acitretin and PUVA therapy in cutaneous LP.
- We found limited evidence for the efficacy of topical corticosteroids and topical retinoids in oral LP.
- We found no evidence that topical calcineurin inhibitors are effective and no evidence that they are more effective than topical corticosteroids in oral LP.

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# Acute urticaria

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## Introduction

This chapter deals with the management of a single isolated episode of urticaria (acute urticaria) rather than recurrent episodes observed in chronic urticaria. Discussion is restricted to randomized controlled trials (RCTs). The majority of the RCTs consider the most recently developed drugs. Earlier experimental work with the first antihistamines is not considered because they were not assessed formally in RCTs. It should be noted that many of the reported RCTs have been conducted in emergency departments. It is unclear whether such results also apply to ordinary practice.

## Background

### Definition

Usual synonyms for urticaria are “hives” or “nettle rash,” according to the German term “Nesselsucht,” which focuses on the typical reactions following skin contact with the stinging nettle (*Urtica dioica*).

The primary lesions of this monomorphic exanthematous disease are hives or wheals, which are defined as circumscribed white- to pink-colored compressible skin elevations produced by dermal edema. Accompanying erythemas in the surrounding area are typical. Pathophysiologically, the wheal can be characterized by local vasodilatation and increase of permeability of capillaries and small venules, followed by transudation of plasma constituents into the papillary and upper reticular dermis. Among a large number of substances, such as kinins, leukotrienes, prostaglandins, or proteolytic enzymes, histamine is the best known elicitor of typical wheal-and-flare reactions. Eruptions of urticarial lesions are usually associated with intense pruritus.

Although the disease may be easily diagnosed from a clinical point of view, standardized or validated diagnostic criteria for urticaria do not exist. The disease is classified by etiology or course.

### Incidence/prevalence

Valid population-based estimates on the incidence of acute urticaria are lacking. Approximately 20–30% of the general population experience at least one episode of urticaria in their life. There is

some consistency in the assumption that acute urticaria is more common in children. Females predominate in acute and chronic forms of the disease [1].

### Etiology

In principle, the same etiological considerations as for chronic urticaria apply. In correspondence with the course of the disease, (acute) infections alone or in combination with concomitant drug intake were found to be associated with acute urticaria in 30–50% of cases [2].

### Prognosis

By definition, acute urticaria is restricted to an occurrence of no longer than 6 weeks, otherwise it will be classified as chronic urticaria. The disease is therefore considered to be self-limiting.

### Diagnostic tests

In principle, the same diagnostic considerations as for chronic urticaria apply. However, a full diagnostic workup is rarely indicated in acute cases. A carefully taken history will provide important etiological hints (infection, drugs).

### Aims of treatment

The aims of treatment are to reduce symptoms or to shorten the course of the disease.

### Relevant outcomes

- Intensity of subjective symptoms (pruritus, sedation);
- disease/wheal intensity;
- general physicians' and patients' assessment as assessed by a numeric scale or a visual analogue scale (VAS);
- surface area (rule of nine);
- cessation rate.

### Methods of search

Any RCT or meta-analysis, systematic review, or Cochrane review on “acute” and “urticaria” or “hive” or “wheal” or “nettle and rash” in the electronic databases PubMed, CENTRAL, and CDSR of the Cochrane Library up to August 2012 were searched. We did not



include studies with healthy volunteers or on experimentally induced histamine reactions.

## Questions

### Which drugs are efficient and safe in the treatment of acute urticaria?

The search of the Cochrane Library and the other electronic databases revealed a recent systematic review on the use of histamine H<sub>2</sub>-receptor antagonists for urticaria by Fedorowicz *et al.* [3]. They included the RCTs of Runge [16], Pontasch [14], Watson [13], and Lin [15], which are described in this chapter as well. A consensus report on the management of urticaria appeared as a result of a panel discussion during the clinically oriented European Society for Dermatological Research's symposium *Urticaria 2000* [4]. Besides the elimination of eliciting stimuli, nonsedating H<sub>1</sub> antihistamines were recommended as standard and initial treatment, with prednisolone 50 mg/day for 3 days as alternative treatment. A further review, which appeared in 2001, describes the evidence-based evaluation of antihistamines in the treatment of urticaria [5]. The paragraph on acute urticaria discusses two studies, which will also be

presented in this chapter [2,6]. Other reviews appeared in 2002, 2003, and 2004 but did not refer to other RCTs than those mentioned in the following [7–9].

Recently, a European consensus guideline on urticaria was published, which also applied methods of evidence-based medicine (systematic literature search, standardized critical appraisal, levels of evidence, and grades of recommendation) [10]. Concerning acute urticaria, nonsedating, second-generation, H<sub>1</sub> antagonists were recommended (grade of recommendation D) based on two publications on loratadine [2] and ceterizine [11] (both level of evidence 2– and low methodological quality). The latter trial was designed to prevent rather than to treat acute urticaria.

Nonresponsive patients should receive either oral corticosteroids as prednisone, 2 × 20 mg/day for 4 days [12] or prednisolone (50 mg/day for 3 days) [2] or alternatively H<sub>2</sub>-blockers (single dose for 5 days) [6,13,14]. Based on levels of evidence 2– and 2+ and a weak methodological quality of one study [2], these therapeutic alternatives were consented with grade D of recommendation.

With respect to single RCTs, the Cochrane Library listed seven such trials with acute urticaria as primary endpoint of the intervention and not as a reported side effect. Three further trials were identified in PubMed. These trials are summarized in Table 28.1.

**Table 28.1** Summary of data from RCTs of the treatment of acute urticaria.

Reference	Intervention	Outcome measures	No. patients enrolled	Results
Moscato and Moore [6]	Single-dose cimetidine 300 mg IM or diphenhydramine 50 mg IM	Itching, wheal intensity, sedation, wheal extent, overall improvement on a 3–4-point numerical scale; validity and reliability not known	93 No dropouts	No difference for clinical response Diphenhydramine significantly more sedating
Watson <i>et al.</i> [13]	Single-dose H <sub>2</sub> -receptor antagonist famotidine 20 mg IM vs H <sub>1</sub> -receptor antagonist diphenhydramine 50 mg IM in the treatment of acute urticaria	Pruritus (patient, VAS) Intensity of urticaria (physician, VAS) Surface area (physician, rule of nine) Sedation (patient, VAS)	25 No dropouts	Only within-group comparison (before/after comparison)
Lin <i>et al.</i> [15]	Diphenhydramine 50 mg + ranitidine 50 mg vs diphenhydramine 50 mg + placebo	Presence of urticaria at baseline and after 1 and 2 h	Unclear	Presence of urticaria after 2 h: 16.2% vs 8.3% (+ ranitidine) <i>P</i> = 0.02
Runge <i>et al.</i> [16]	Single-dose diphenhydramine 50 mg + placebo IV or cimetidine 300 mg + placebo IV or diphenhydramine 50 mg + cimetidine 300 mg IV	Extent (number of involved areas) VAS (110 mm) to assess: pruritus – throat tightness and facial swelling (patient) urticaria – pharyngeal tissue swelling and facial swelling (physician) Change of 25 mm considered clinically significant Adverse effects	39	More urticaria patients receiving diphenhydramine + cimetidine (11/12) experienced relief compared with those receiving diphenhydramine (5/11, <i>P</i> = 0.027) or cimetidine (8/10, ns) alone
Simons [11]	Oral cetirizine 0.25 mg/kg twice daily vs placebo over 18 months in children with atopic eczema	Incidence of diary-reported symptoms typical for acute urticaria	795	Cumulative incidence of urticaria 16.2% vs 5.8% during 18-month treatment ( <i>P</i> < 0.001) 4.6% vs 3.0% during 6-month follow up (ns)
Pollack and Romano [12]	Single-dose diphenhydramine 50 mg IM followed by oral hydroxyzine 25 mg every 4–8 h plus oral prednisone 20 mg twice daily for 4 days or placebo	Pruritus (VAS 10 cm) Adverse effects	43	Significantly more improvement with the addition of steroid
Zuberbier <i>et al.</i> [2]	Loratadine 10 mg/day until remission vs prednisolone 50 mg/day for 3 days followed by loratadine 10 mg/day until remission	Cessation of whealing	109	Percentage cessation at 5 time points Significant differences only after 3 days (when the intervention arm had received prednisolone only so far) (93.8% vs 65.9%)

ns, not significant; IV, intravenous; IM, intramuscular.

### Antihistamines (first-generation H<sub>1</sub> antagonists and H<sub>2</sub> antagonists)

Four studies compared the use of H<sub>1</sub> and H<sub>2</sub> antagonists or a combination. None of these studies had a placebo arm. Two studies compared diphenhydramine with an H<sub>2</sub> antagonist (famotidine or cimetidine).

Moscatti and Moore investigated the efficacy of a single-dose of intramuscular cimetidine 300 mg with intramuscular diphenhydramine 50 mg in 93 young adults [6]. Both treatments yielded significant reductions in itching, wheal intensity, and extent after 30 min, with no differences between treatments. A significant increase in sedation was reported by patients in both groups, but was significantly higher in patients treated with diphenhydramine. Absolute changes in the three- and four-point scoring scales appeared to be clinically important. The study is limited by flaws in the process of randomization and blinding.

Watson *et al.* compared single-dose intramuscular diphenhydramine 50 mg with intramuscular famotidine 20 mg in 25 adults [13]. After 30 min, pruritus was reduced significantly by both treatments, with diphenhydramine appearing more effective. Famotidine also significantly reduced the affected body surface area. Physician-rated intensity of urticaria was reduced equally and significantly by both drugs. A nonsignificant increase in sedation was reported by patients receiving diphenhydramine. The small sample size and unbalanced group size (diphenhydramine  $n = 10$ , famotidine  $n = 15$ ; no block randomization) do not allow for a meaningful comparison of the groups.

Lin *et al.* compared the efficacy of single-dose intravenous diphenhydramine 50 mg alone or in combination with intravenous ranitidine 50 mg in 91 adults [15]. Significantly more patients receiving the combination therapy (91.7%) were free of symptoms after 2 h compared with those who received diphenhydramine alone (73.8%). After control for baseline extent, the combination therapy was able to reduce the number of involved areas significantly within 2 h. Significantly more additional antihistamines were administered in the diphenhydramine group, however, which may have shifted the effect towards the zero-effect level.

Runge *et al.* studied 39 adults with acute allergic reactions, including urticaria [16]. Fourteen patients received a single dose of intravenous diphenhydramine 50 mg, 12 received intravenous cimetidine 300 mg, and 13 received both preparations. After 30 min, the combination therapy led to significantly higher reduction of urticaria (evaluated using a VAS) compared with diphenhydramine alone. The latter, however, achieved the best results in reduction of pruritus, differences being significant compared with cimetidine. The study is limited by the small sample size and significant differences in mean treatment scores for urticaria between study groups, which were not adjusted for in later analyses.

Pontasch *et al.* compared three oral medication in the treatment of acute urticaria in adults [14]. Seven patients received diphenhydramine, six received famotidine, and another seven received cromolyn sodium. Patient satisfaction was highest with diphenhydramine (6/7), followed by famotidine (3/6) and cromolyn sodium (3/7). Adverse effects were reported in 3/7 treated with diphenhydramine, in 3/6 of the famotidine group, and in one patient who received cromolyn sodium.

### Corticosteroids

The addition of oral prednisone 20 mg twice daily for 4 days to the standard treatment with H<sub>1</sub> antagonists was investigated in 43 adults by Pollack and Romano [12]. The intensity of itch, as scored

on a VAS, was significantly reduced by both regimens after 2 and 5 days of follow-up. However, the addition of prednisone reduced the symptom score significantly more than the standard therapy. Although standard therapy with antihistamines is generally considered sufficient, in selected cases (severity, need to shorten antihistamines) addition of prednisone seems helpful.

Similar, Zuberbier *et al.* showed that prednisolone 50 mg/day for 3 days led to a significantly higher clearing rate (93.8%) after 3 days than therapy with loratadine 10 mg/day in 109 patients [2]. The study may be limited by aspects of design (open, pseudo-randomization by consecutive time periods, differential allocation of possibly pregnant women).

A best-evidence report of 2004 summarizes both studies mentioned above [17].

### Other treatments and nonrandomized trials

An early case series of five patients with acute urticaria following insect stings reported good therapeutic effects of intravenous cimetidine 300 mg initially followed by 300 mg orally four times daily) after ineffective administration of epinephrine (adrenaline), H<sub>1</sub> antagonists, and corticosteroids [18].

A further report investigated the effect of flunarizine, a calcium antagonist, in the treatment of acute urticaria. In this uncontrolled trial, 20 patients received a single 10 mg sublingual dose of flunarizine. After 3 h, 16 patients had improved, with effects being more pronounced for itching than for reduction of wheals. Four patients remained unresponsive and five other patients reported drowsiness as a major side effect [19].

A Chinese publication describes the therapeutic effect of the added ingredient of *Radix angelicae sinensis* in 106 patients with acute urticaria. Unfortunately, the lack of an abstract in English makes it difficult to draw conclusions [20].

### Prevention

The European multicenter study ETAC (Early Treatment of the Atopic Child) investigated the preventive effect of long-term (18 months) administration of cetirizine 0.25 mg/kg twice daily in 1–2-year-old children with atopic eczema and positive family history of allergies [11]. On addition to the primary endpoint (asthma), symptoms typical for acute urticaria were recorded in a diary during the intervention period and a 6-month follow-up. During the intervention period, significantly fewer episodes of acute urticaria (5.8%) were reported in the intervention group compared with the placebo arm (16.2%). This effect did not persist after medication was stopped (3.0% vs 4.6%).

### Harms

On the basis of the available studies on acute urticaria, the major side effect is sedation associated with the first-generation H<sub>1</sub> antagonists. Chapter 29 on chronic urticaria discusses the newer antihistamines.

### Comment: implications for clinical practice

Generally, the available therapeutic evidence for acute urticaria is quantitatively and qualitatively weak. RCTs of the therapeutic efficacy of the second-generation antihistamines are lacking, although one would like to consider these the first choice of therapy based on the studies in chronic urticaria. There is some evidence that the combination of H<sub>1</sub> and H<sub>2</sub> antagonists has additional beneficial effects. A short-term intervention with corticosteroids seems to be superior to a treatment with antihistamines alone, but should be considered in the context of individual needs.

### Key points

- Acute urticaria is a common disease.
- It seems to predominate in children and females.
- The etiology remains mostly unclear, but there is evidence that (acute) infections and concomitant drugs, as well as (food) hypersensitivity, are important elicitors.
- The therapeutic evidence for treatment of acute urticaria is qualitatively and quantitatively poor.
- There is evidence that first- and second-generation antihistamines are effective and that the combination with H<sub>2</sub> antagonists may have additional beneficial effects.
- A short-term intervention with corticosteroids seems to be superior to a treatment with antihistamines alone, but should be considered in the context of individual needs.

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# Chronic urticaria

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## Background

### Definition and classification

Urticaria is characterized by the development of wheals (hives), angioedema, or both [1]. Whereas wheals (Figure 29.1) are usually associated with pruritus and resolve within 24 h, angioedema is a deeper swelling of the lower dermis and subcutis, which may be painful rather than itchy and can take up to several days to resolve [1]. Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both occur [1]; for example, anaphylaxis, urticarial vasculitis, auto-inflammatory syndromes, or bradykinin-mediated angioedema, such as hereditary angioedema or ACE-inhibitor-induced angioedema.

Chronic urticaria is defined by recurrently appearing signs and symptoms for more than 6 weeks [1]. It is subdivided into chronic spontaneous urticaria (CSU), where symptoms occur spontaneously, and inducible forms (chronic inducible urticaria – CIndU), such as physical urticaria and cholinergic urticaria [1]. In CIndU, specific triggers (e.g., cold contact in cold urticaria) provoke urticaria symptoms. The current classification [1] is shown in Table 29.1. Notably, more than one subform of chronic urticaria can occur in the same patient. For example, CSU is frequently accompanied by physical urticaria such as symptomatic dermographism or delayed pressure urticaria.

Chronic urticaria severely impairs the quality of life of affected subjects. Patients with CSU suffer a comparable degree of impairment in many aspects as patients with severe coronary artery disease waiting for bypass surgery [2]. In comparison with other skin diseases, CSU has been repeatedly shown to be among those disorders associated with a particular strong quality-of-life impairment [3].

### Incidence/prevalence

Chronic urticaria is one of the most frequent skin diseases. Data from the middle of the last century suggest that around every fifth person will experience at least one episode of any type of urticaria during her or his lifetime [4, 5]. In 1972, Hellgren reported a point prevalence of around 0.1% for chronic urticaria in the total population in Sweden [6]. More recent population-based studies reported a point prevalence of 0.6% for CSU in Spain [7] and a period prevalence of 0.8% in 1 year for chronic urticaria in Germany [8]. Women suffer from chronic urticaria about twice as often as men do [3].

The exact incidence and prevalence of CIndU is not well examined. However, its subforms differ considerably in frequency, with symptomatic dermographism and cholinergic urticaria being more prevalent than other subtypes, such as cold urticaria and delayed pressure urticaria. Heat urticaria, solar urticaria, aquagenic urticaria, and vibratory angioedema are rare disorders. The disease activity of all chronic urticaria subtypes can markedly change over time and differ between individual patients. In addition, some inducible forms predominantly occur in certain age groups. For example, cholinergic urticaria has its peak incidence in young adults and, when including also very mild forms, affects up to 20% of people at the end of their 20s [9].

### Etiology

Chronic urticaria is a mast-cell-driven disease. Its signs and symptoms, both in spontaneous and inducible urticaria, develop after the activation and degranulation of skin mast cells and the subsequent release of proinflammatory mediators. Mast cells contain pre-formed histamine, heparin, proteases (e.g., tryptase, chymase) and several cytokines that are immediately released upon activation. But mast cells are also able to rapidly produce and secrete prostaglandins, leukotrienes, and platelet-activating factor (PAF). The released mediators result in sensory nerve activation, vasodilatation, and plasma extravasation as well as lesional cell recruitment [1], thereby leading to the typical urticaria symptoms pruritus, wheals, and angioedema. Whereas the pathogenic mechanisms at the level or downstream of mast cells are well understood, with histamine and its interaction with the H<sub>1</sub>-receptor playing a critical role, the mechanisms of mast cell activation are still largely unknown. An allergic activation with the binding of environmental allergens to skin mast-cell-bound specific immunoglobulin E (IgE) is only very rarely relevant in chronic urticaria. Therefore, it can usually not be classified as an allergic disorder. Instead, reported candidates for causing mast cell activation comprise autoantibodies to IgE or the IgE receptor, IgE autoantibodies directed against autoantigens (autoallergens), complement components such as C5a, as well as neuropeptides (e.g., substance P).

### Prognosis

The natural course of chronic urticaria varies considerably between patients. In most patients chronic urticaria is of long duration, frequently lasting for several years [3]. One of the few studies inves-





**Figure 29.1** Wheals on the thorax of young man with CSU.

**Table 29.1** Classification of chronic urticaria.<sup>a</sup>

Chronic urticaria	
Chronic urticaria subtypes	Specific symptom-eliciting factors
Chronic spontaneous urticaria	None (spontaneous appearance of wheals, angioedema or both due to known or unknown causes)
Inducible urticarias	
Physical urticarias	
<ul style="list-style-type: none"> <li>• Symptomatic dermographism<sup>1</sup></li> <li>• Cold (contact) urticaria</li> <li>• (Delayed) pressure urticaria</li> <li>• Solar urticaria</li> <li>• Heat (contact) urticaria</li> <li>• Vibratory angioedema</li> </ul>	<ul style="list-style-type: none"> <li>• Scratching/shear force</li> <li>• Exposure to cold<sup>b</sup></li> <li>• Vertical pressure</li> <li>• Exposure to UV and/or visible light</li> <li>• Exposure to heat</li> <li>• Exposure to vibration</li> </ul>
Cholinergic urticaria	Rise in body temperature <sup>c</sup>
Contact urticaria	Individual substances
Aquagenic urticaria	Contact with water

<sup>a</sup>Also called urticaria factitia, dermographic urticaria.

<sup>b</sup>For example, cold air, cold liquids, or objects.

<sup>c</sup>For example, after/during physical exercise.

tigating the duration of chronic urticaria in the total population [7] found half of the patients to be symptom free 3 months after onset of disease and four of five patients after 1 year. However, more than 10% still had the disease after 5 years. Several other authors have examined disease duration in CSU in selected populations. Although their data vary greatly, a considerable proportion of patients was found to exhibit a disease duration of more than 5 years [10–13] or even more than 10 years [10, 13].

As of yet, there is no prognostic marker available that helps to predict the individual duration of disease. However, there are some factors that appear to be associated with a long duration of chronic urticaria, such as disease severity, appearance of angioedema, a

combination of CSU with CIndU, and autoreactivity (positivity in the autologous serum skin test (ASST)) [3]. Some physicians believe that symptomatic therapy that results in the complete control of symptoms can shorten the course of disease, but there is no published evidence to support this [3].

### Diagnostic tests and possible underlying causes

The diagnostic workup in patients with chronic urticaria is to (1) exclude differential diagnoses if indicated, (2) exclude severe inflammatory conditions (in CSU), (3) test for the presence of CIndU subforms (based on clues from the history), (4) identify the causes of disease (in severe and/or long-standing CSU), and (5) assess disease activity, disease control, and impact.

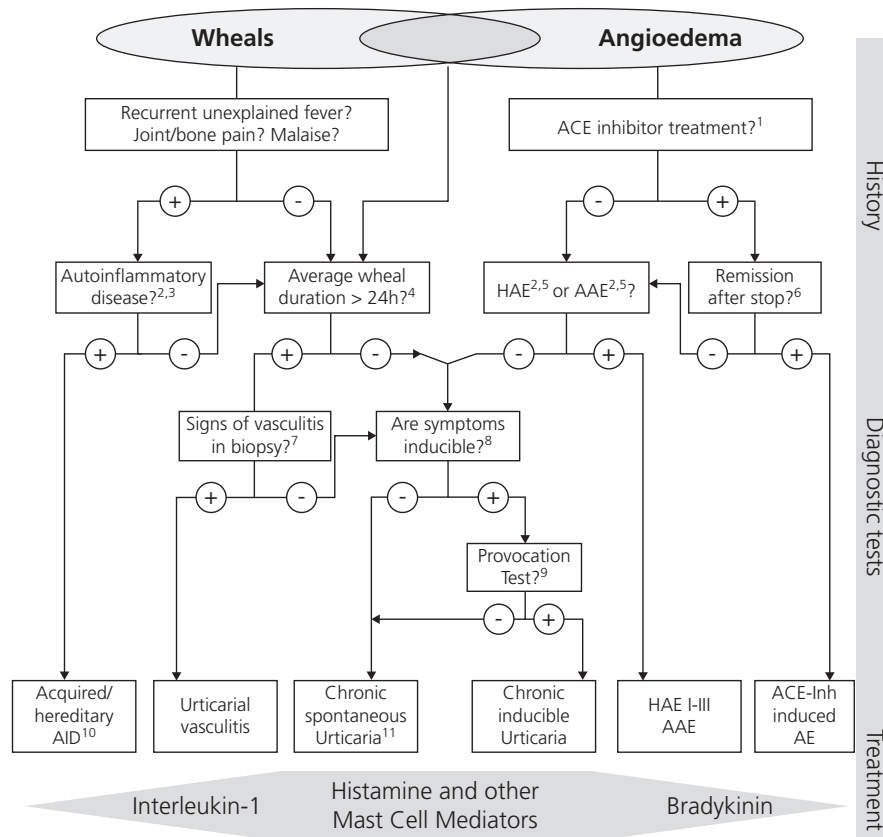
The current EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines [1] provide a helpful algorithm for the diagnosis and differential diagnosis of patients with chronic urticaria symptoms; that is, wheals and/or angioedema (Figure 29.2).

If the diagnosis of CSU is assured, the general recommendation is to first perform a thorough history and physical examination and to rule out severe systemic disease by basic laboratory tests. These should include a differential blood count and the determination of C-reactive protein (CRP)/ erythrocyte sedimentation rate (ESR). In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) should be omitted [1]. Extended diagnostic procedures should be conducted in patients with long-standing and/or severe disease based on the patient's individual history [1]. Intensive and costly general screening programs are strongly advised against [1]. The current recommendations for diagnostic tests to be performed in chronic urticaria are depicted in Table 29.2.

Common possible causes of CSU include autoreactivity, autoallergy, chronic infections, and intolerance to food components. The frequency of these causes may vary between different geographical regions. Patients with autoreactive CSU are characterized by circulating histamine releasing factors leading to a positive ASST [14]. Around one-third to half of all CSU patients are ASST positive [14, 15]. Some of these patients exhibit autoantibodies against IgE or the high-affinity IgE receptor [14]. High disease activity, poor response to H<sub>1</sub>-antihistamine therapy, and autoimmune comorbidities may point towards the presence of autoreactive CSU. In addition, some CSU patients exhibit IgE antibodies to autoantigen (autoallergens) such as thyroperoxidase [16] and double-stranded DNA [17], and anti-IgE therapy has been shown to effectively control disease in CSU patients with anti-autoantigen IgE [18].

There is a broad consensus that chronic infections with bacteria, viruses, fungi, and helminths are potential causes of CSU [1]. It is possible that infections are either associated with CSU or just coincidence. A causal relationship between an infection and CSU in individual patients will only become clear after specific treatment. There are several reports that demonstrate a clear benefit of CSU patients after eradication of infectious processes [19, 20]. These underlying infections may be asymptomatic or associated with only mild symptoms. In some of these patients no systemic signs of inflammation are detectable.

Intolerance to foods is another common cause of CSU, which must not be mixed up with food allergies that only very rarely underlie the disease. CSU due to intolerance is usually confirmed by a documented improvement of urticaria symptoms during a 4-week pseudoallergen-low diet and by a worsening of disease after oral provocation with the suspected food components. Beneficial effects of a pseudoallergen-low diet have been demonstrated in 32–73% of CSU patients [21–23]. Importantly, the effect of a



**Figure 29.2** Recommended diagnostic algorithm for patients presenting with wheals, angioedema, or both.<sup>1</sup> Abbreviations: AAE, acquired angioedema due to C1-inhibitor deficiency; ACE-Inh, angiotensin converting enzyme inhibitor; AE, angioedema; AH, antihistamine; AID, auto-inflammatory disease; HAE, hereditary angioedema; IL-1, interleukin-1 [24].

<sup>1</sup> Other (new) drugs may also induce bradykinin-mediated angioedema.

<sup>2</sup> Patients should be asked for a detailed family history and age of disease onset.

<sup>3</sup> Test for elevated inflammation markers (CRP, ESR), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g., cryopyrin-associated periodic syndrome), if strongly suspected.

<sup>4</sup> Patients should be asked: "How long do your wheals last?"

<sup>5</sup> Test for complement C4, C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis if former tests are unremarkable but patient's history suggests hereditary angioedema.

<sup>6</sup> Wait for up to 6 months for remission; additional diagnostics to test for C1-inhibitor deficiency should only be performed if the family history suggests hereditary angioedema.

<sup>7</sup> Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV (urticarial vasculitis)?

<sup>8</sup> Patients should be asked: "Can you make your wheals come?"

<sup>9</sup> In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations [103] should be performed.

<sup>10</sup> Acquired AIDs (autoinflammatory syndromes) include Schnitzler's syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary AIDs include cryopyrin-associated periodic syndromes (CAPS) such as familial cold auto-inflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS).

<sup>11</sup> In some rare cases recurrent angioedema is neither mast cell mediator-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors.

pseudoallergen-low diet seems not to be predictable based on patient history.

Other infrequent causes of CSU comprise other chronic inflammatory conditions as well as, very infrequently, sensitizations to type I allergens.

In CIndU the routine diagnosis mainly aims at the identification of the subtype by the appropriate provocation tests and the determination of trigger thresholds [1] (Table 29.2). The latter allows for assessing disease status and response to treatment [1]. The actual

underlying causes of CIndUs, with the exception of contact urticaria, are unknown. Therefore, examinations for causes are not recommended, unless there are compelling clues from the patient history.

In addition, it is important to determine and monitor chronic urticaria patients for disease activity, disease control, and health-related quality-of-life impairment at the beginning and during the course of disease. The currently available and validated instruments for these purposes are shown in Table 29.3.

**Table 29.2** Recommended diagnostic tests in chronic urticaria patients.<sup>a</sup>

Chronic urticaria subtype	Routine diagnostic workup	Extended diagnostic program <sup>a</sup>
Chronic spontaneous urticaria	Differential blood count, ESR or CRP. Omission of suspected drugs (e.g., NSAIDs)	Tests (no preferred order) for infectious diseases (e.g., <i>Helicobacter pylori</i> ), type I allergy; functional autoantibodies; thyroid hormones and autoantibodies, skin tests including physical tests, intolerance by suggesting a pseudoallergen-low diet for 3–4 weeks, tryptase, autologous serum skin test, lesional skin biopsy
Inducible urticarias		
Symptomatic dermographism <sup>a</sup>	Elicit dermographism and perform threshold test (e.g., with a dermatographometer, FricTest device [104])	Differential blood count, ESR or CRP
Cold (contact) urticaria	Cold provocation and threshold test (e.g., with ice cube test or Temptest device [105, 106])	Differential blood count, ESR or CRP, cryoproteins to rule out other diseases, especially infections
(Delayed) pressure urticaria	Pressure test and threshold test (e.g., with weighted rods or dermatographometers). Test result should be read 6 h after testing	None
Solar urticaria	Provocation with UV and visible light of different wave lengths and threshold test (determine test results 15–20 min after provocation)	Rule out other light-induced dermatoses
Heat (contact) urticaria	Heat provocation and threshold test (e.g., with hot water bath or Temptest device [105, 106])	None
Vibratory angioedema	Provocation with vibratory device (e.g., with a laboratory vortex mixer)	None
Cholinergic urticaria	Exercise (e.g., using an ergometer) and/or hot bath provocation	None
Contact urticaria	Provocation test of suspected substance with immediate reading; e.g., prick test	None
Aquagenic urticaria	Cutaneous provocation test with wet cloths at body temperature applied for 20 min	None

<sup>a</sup>Suggested to be based on clues from patient history in order to identify underlying causes or eliciting factors and for ruling out possible differential diagnoses.

**Table 29.3** Available validated and specific tests to determine disease activity, disease control, and disease/symptom-specific quality of life in patients with chronic urticaria.

	Chronic spontaneous urticaria			Inducible urticaria
	Patients with wheals	Patients with wheals and angioedema	Patients with angioedema	
Disease activity	UAS [1, 107]	UAS [1, 107] and AAS [108]	AAS [108]	Determination of trigger threshold with specific provocation test [1]
Disease control	UCT [109]	UCT [109]	UCT [109]	UCT [109]
Quality of life	CU-Q <sub>2</sub> oL [110]	CU-Q <sub>2</sub> oL [110] and AE-QoL [110]	AE-QoL [111]	—

UAS, urticaria activity score; AAS, angioedema activity score; UCT, urticaria control test; CU-Q<sub>2</sub>oL, chronic urticaria quality of life questionnaire; AE-QoL, angioedema quality of life questionnaire.

## Aims of treatment

The aim of treatment is to achieve complete symptom control as safely as possible [1], either by curing patients or by preventing wheal and/or angioedema formation as well as pruritus, and thereby also resolving sleep disturbance and improving patients' health-related quality of life.

## Relevant outcomes

- Level of disease control;
- urticaria activity;
- angioedema activity;

- quality of life;
- interference with sleep;
- interference with daily activities;
- permanent remission.

## Methods of search

A search for clinical studies on “urticaria” was carried out by searching the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Database of Systematic Reviews (CDSR) of the Cochrane Library. In addition, a hand-search was performed.

## Questions

### Which drugs are effective in chronic urticaria?

The updated guidelines [1] published in 2014 revised the recommendations for chronic urticaria management based on the available evidence and suggested an algorithm for the best possible symptomatic treatment approach (Figure 29.3). As first-line therapy, the use of H<sub>1</sub>-antihistamines in standard, licensed dose is recommended. Modern second-generation H<sub>1</sub>-antihistamines should be preferred over first-generation H<sub>1</sub>-antihistamines, because of strong evidence regarding potential serious side effects of the latter. If symptoms persist after 2 weeks, a trial of up to fourfold dosed second-generation H<sub>1</sub>-antihistamines is recommended as second-line therapy. It is also recommended to preferably increase the dose with a single drug instead of combining different H<sub>1</sub>-antihistamines at the same time. If symptoms still persist after a further 1–4 weeks, omalizumab, ciclosporin, or montelukast should be added as third-line therapeutics. There is strong advice against the long-term use of systemic corticosteroids in urticaria, but a short course to control acute exacerbation may be tried. In the following, the currently available evidence for the guideline recommended treatment options are reviewed in detail.

### Efficacy

#### Second-generation H<sub>1</sub>-antihistamines in licensed dose

Second-generation H<sub>1</sub>-antihistamines are the first-line treatment option for patients with all forms of chronic urticaria. They belong to the most frequently taken drugs and generally have a good safety profile. H<sub>1</sub>-antihistamines are currently the only licensed treatment for urticaria together with omalizumab (anti-IgE), and their clinical efficacy and safety is well documented in numerous randomized controlled trials (RCTs). This is clear and accepted and, therefore, not reviewed in detail here. Also, a systematic review of second-generation H<sub>1</sub>-antihistamines in urticaria treatment is forthcoming from the Cochrane Collaboration. Notably, recent reports have demonstrated that second-generation antihistamines in licensed standard doses lead to a complete remission of urticaria symptoms in less than 50% of CSU patients [3, 25]. This is also the experience of the treating physicians in private practice [26] and in the tertiary care setting [27]. In general, patients should be advised to use H<sub>1</sub>-antihistamines continuously rather than on demand, since this has been shown to be the more effective treatment approach in CSU [28] and is also supported by their mechanism of action; that is, that they are inverse agonists of the histamine H<sub>1</sub>-receptor, shifting its conformation towards the inactive state [1]. The dosage in children over 12 years is usually the same as that for adults; the manu-

facturers' recommendations should be followed for children aged up to 12 years.

#### Increasing the dose of second-generation H<sub>1</sub>-antihistamines

An “updosing” of second-generation H<sub>1</sub>-antihistamines is recommended when the standard, licensed dose is not sufficient to achieve symptom control in chronic urticaria patients [1]. For this approach there is currently no systematic review available, but it is supported by several independent RCTs (Table 29.4), four of which [29–32] were performed in CSU patients. Two [30, 32] trials were explicitly done in order to test the efficacy of H<sub>1</sub>-antihistamine updosing. Staevska *et al.* [32] examined 80 patients unresponsive to standard dosed H<sub>1</sub>-antihistamines in a dose escalation, crossover trial with desloratadine and levocetirizine. With licensed doses (5 mg), 13 of 80 patients became symptom free, and an additional 28 of the remaining subjects reportedly showed complete response when treated with up to 20 mg. Seven of these 28 patients showed complete remission only after changing treatment from desloratadine 20 mg to levocetirizine 20 mg. The updosed H<sub>1</sub>-antihistamines did not increase somnolence, and no adverse events (AEs) requiring discontinuation of treatment occurred during the study. In the study of Gimenez-Arnau *et al.* [30], the data of 538 patients from two multicenter RCTs [33, 34], examining rupatadine at the licensed 10 mg or increased 20 mg dose, were pooled and examined for proportions of responders. A reduction of symptoms by at least 75% was observed in 14% of patients treated with placebo and in 35% and 48% treated with rupatadine 10 mg and 20 mg, respectively. The difference between rupatadine treatment and placebo as well as between rupatadine 20 mg and 10 mg was statistically significant. The other two available RCTs in CSU were dose ranging studies applying fexofenadine in doses from 20 to 240 mg twice daily with a total of 876 patients [29, 31]. These studies both found a significant linear trend regarding the reduction of urticaria symptoms with increasing fexofenadine doses. Fexofenadine 240 mg showed the strongest effects in most outcome measures. However, the direct comparison of the higher doses with the regular dose (60 mg twice daily) exhibited no significant differences. A possible reason for not finding stronger effects of updosing in these two trials might be the fact that patients with a history of unresponsiveness to prior H<sub>1</sub>-antihistamine therapy were excluded from participation so that the response to regular dosed H<sub>1</sub>-antihistamines might be overestimated. In both studies, there were no dose-related trends in the incidence of AEs.

Apart from these RCTs, there are two uncontrolled, open-label studies [35, 36] in patients with CSU unresponsive to standard dosed H<sub>1</sub>-antihistamines. While the first of these investigations found only 1 of 20 patients to benefit from an updosing of cetirizine [35], the second study in 21 subjects found the efficacy of 20 mg cetirizine on urticaria symptoms to be significantly better compared with the regular 10 mg dose [36].

Finally, three survey studies assessed the real-life experience with H<sub>1</sub>-antihistamine updosing in physicians of the primary and secondary care levels [26], in physicians of the tertiary care level [27], and in patients [37]. All three reported a higher efficacy of updosed H<sub>1</sub>-antihistamines in CSU patients compared with standard dose treatment.

In addition to these studies in CSU, there are three small RCTs available comparing regular dosed and updosed desloratadine [38, 39] and bilastine [40] in a total of 83 patients suffering from cold urticaria. All three trials found that updosing increased the efficacy of H<sub>1</sub>-antihistamine treatment and was well tolerated.

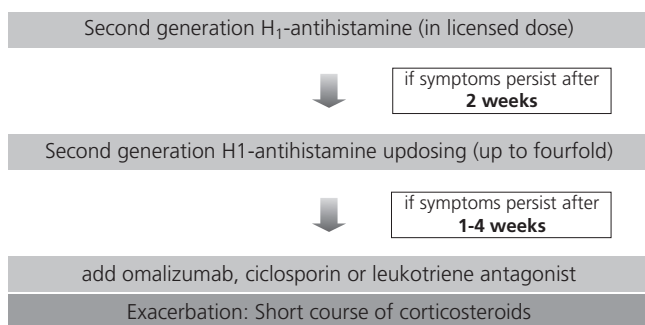


Figure 29.3 Recommended treatment algorithm for urticaria [1].



**Table 29.4** H<sub>1</sub>-antihistamine updosing in chronic urticaria – available RCTs comparing regular licensed doses with higher doses.

Author	Year	Disease examined	Sample size <i>n</i>	Age of patients	Treatment	Treatment duration	Study design	Main results
Krause <i>et al.</i> [34]	2013	Cold urticaria	20	Adults	Bilastine 20 mg vs 40 mg, vs 80 mg, vs placebo	1 week for each dose	Randomized, double-blind, crossover, placebo-controlled, monocenter study	Bilastine 20 mg was effective in reducing the critical temperature threshold. <sup>a</sup> Updosing to 80 mg increased its efficacy. During bilastine, 35% of patients became symptom free during 40 mg and 80 mg 55% and 60%. Bilastine was well tolerated without evidence of increased sedation during dose escalation.
Magerl <i>et al.</i> [38]	2012	Cold urticaria	30	Adults	Desloratadine 5 mg (constant dose) vs 5 mg, 10 mg, 20 mg (dose escalation)	6 weeks	Randomized, double-blind, controlled, dose-escalation, two-center study	Desloratadine 5 mg significantly reduced the critical temperature threshold <sup>a</sup> compared with baseline values (no treatment). Dose escalation resulted in increased efficacy. Complete remission was obtained in none of the patients on 5 mg, while 2 of 15 subjects and an additional 3 of the remaining 13 patients became symptom free on 10 mg and 20 mg. One drug related AE was reported during the trial (mild fatigue during treatment with desloratadine 10 mg).
Staevska <i>et al.</i> [32]	2010	CSU (unresponsive to regular dosed antihistamines)	80	Adults	Desloratadine or levocetirizine in doses of 5 mg, 10 mg and 20 mg (dose escalation depending on efficacy)	4 weeks	Randomized, controlled, double-blind, dose-escalation, crossover, monocenter study	13 of 80 patients became symptom free at the licensed doses and an additional 28 of the remaining patients during up dosing to up to 20 mg. Increased doses went along with an improved quality of life. No AEs occurred requiring discontinuation of treatment, and high dosing did not increase somnolence.
Gimenez-Arnau <i>et al.</i> [30]	2009	CSU	538	Adults	Rupatadine 10 mg vs 20 mg vs placebo	4 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	A reduction of symptoms by at least 75% during treatment was observed in 14% (placebo), 35% (10 mg) and 48% (20 mg). The differences between 10 mg and placebo as well as between rupatadine 10 mg and 20 mg were statistically significant.
Siebenhaar <i>et al.</i> [39]	2009	Cold urticaria	33	Adults	Desloratadine 5 mg vs 20 mg vs placebo	1 week for each dose	Randomized, double-blind, crossover, placebo-controlled, monocenter study	Desloratadine 5 mg and 20 mg significantly reduced cold-induced urticaria symptoms compared with placebo. Updosing to 20 mg showed higher efficacy than 5 mg treatment. Complete protection of symptoms was found during treatment in 3% (placebo), 23% (5 mg), and 50% (20 mg). No increased rate of somnolence or other AEs occurred during high-dose (20 mg) therapy.
Nelson <i>et al.</i> [31]	2000	CSU	437	12 years and older	Twice-daily fexofenadine 20 mg vs 60 mg vs 120 mg vs 240 mg vs placebo	4 weeks	Randomized, double-blind, dose-ranging, parallel group, multicenter study	Each of the fexofenadine doses was statistically superior to placebo in reducing urticaria symptoms with a mild but significant linear trend for improvement with increasing doses, but in the direct comparison of groups the efficacy results were similar in the 60, 120, and 240 mg treated patients. AEs were reported with similar incidence in all treatment groups (no dose dependency).
Finn <i>et al.</i> [29]	1999	CSU	439	12 years and older	Twice-daily fexofenadine 20 mg vs 60 mg vs 120 mg vs 240 mg vs placebo	6 weeks	Randomized, double-blind, dose-ranging, parallel group, multicenter study	Each of the fexofenadine doses was statistically superior to placebo in reducing urticaria symptoms with a mild but significant linear trend for improvement with increasing doses, but in the direct comparison of groups the efficacy results were similar in the 60, 120, and 240 mg treated patients. AEs were reported with similar incidence in all treatment groups (no dose dependency).

CSU, chronic spontaneous urticaria.

<sup>a</sup>Critical temperature threshold: the minimal eliciting temperature of symptoms.

## Omalizumab

Omalizumab is a humanized antibody targeting circulating IgE. As of yet, no systematic review has been published on its use in CSU, but there are five RCTs [18, 41–44] (Table 29.5) that all found high efficacy of omalizumab in CSU subjects who remain symptomatic despite H<sub>1</sub>-antihistamine treatment in licensed doses [18, 41, 43, 44] or even treatment with H<sub>1</sub>-antihistamines at up to four times the licensed dose plus H<sub>2</sub>-antihistamines, leukotriene antagonists, or both [42]. One RCT was a proof-of-concept study restricted to CSU subjects exhibiting IgE antibodies against thyroperoxidase [18], while the others were performed in CSU patients without a particular pre-screening for autoallergy or autoreactivity [41–44]. The first two RCTs published by Gober *et al.* [41] and Maurer *et al.*

[18] applied the dosing regimen established for omalizumab treatment of severe asthma (depending on the patient's weight and IgE levels), for which it is licensed. Both trials found omalizumab to strongly decrease urticaria symptoms compared with placebo. The study of Gober *et al.* [41] was performed in a limited number of 20 subjects that were treated for 6 months and has only been published as an abstract. In the study of Maurer *et al.* [18], 49 patients received treatment for a period of 24 weeks. At the end of this period, 59% of omalizumab-treated patients were completely free of symptoms compared with 14% in the placebo group. A marked reduction of symptoms appeared already in the first week of therapy with a continuing decrease through week 24. The incidence of suspected drug-related AEs was similar in both treatment groups. No

**Table 29.5** Omalizumab treatment in chronic urticaria – available RCTs.

Author	Year	Disease examined	Sample size <i>n</i>	Age of patients	Treatment	Treatment duration	Study design	Main results
Kaplan <i>et al.</i> [42]	2013	CSU (symptomatic despite treatment with H <sub>1</sub> -antihistamines at up to 4 times the licensed dose plus H <sub>2</sub> -antihistamines, leukotriene antagonists, or both	335	12 years and older	4 weekly omalizumab 300 mg vs placebo	24 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Urticaria symptoms and health-related quality of life significantly improved during omalizumab treatment compared with placebo. Complete remission was achieved in 4% (placebo) and 34% (omalizumab 300 mg). Incidence and severity of AEs were similar between both treatment groups. There was no evidence of any clinically meaningful trends in laboratory parameters or vital signs associated with omalizumab therapy and no patient developed anti-omalizumab antibodies.
Maurer <i>et al.</i> [43]	2013	CSU (unresponsive to regular dosed antihistamines)	323	12 years and older	4 weekly omalizumab, 75 mg vs 150 vs 300 mg vs placebo	12 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Urticaria symptoms and health-related quality of life significantly improved during omalizumab 150 mg and 300 mg treatment as compared to placebo. The strongest effects were observed for the 300 mg dose. No difference was found between 75 mg and placebo. Complete remission was achieved in 5% (placebo), 16% (75 mg), 22% (150 mg) and 44% (300 mg). Proportions of patients with at least one AE were similar across the treatment groups.
Saini <i>et al.</i> [44]	2011	CSU (unresponsive to regular dosed antihistamines)	90	12 years and older	Single-dose omalizumab 75 mg vs 300 mg vs 600 mg vs placebo	Single-dose treatment, efficacy analysis after 4 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Urticaria symptoms significantly improved after 300 mg and 600 mg treatment compared with placebo. No difference was found between 75 mg and placebo. 600 mg had less pronounced effects compared with 300 mg. Complete remission was achieved in 0% (placebo), 4% (75 mg), 36% (300 mg), and 29% (600 mg). The incidence of AEs was similar across treatment groups with the majority of AEs being mild to moderate.
Maurer <i>et al.</i> [3, 18]	2011	CSU with IgE autoantibodies against TPO (unresponsive to regular dosed antihistamines)	49	Adults	Omalizumab 75–375 mg (asthma dosing scheme) vs placebo	24 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Urticaria symptoms and health-related quality of life significantly improved during omalizumab treatment compared with placebo. A marked reduction of symptoms was found already in the first week of therapy. Complete remission was achieved in 14% (placebo) and 59% (omalizumab). <i>Safety:</i> the incidence of suspected drug-related AEs was similar between both treatment groups.
Gober <i>et al.</i> [40]	2008	CSU (unresponsive to regular dosed antihistamines)	20	Not reported	Omalizumab (asthma dosing scheme) vs placebo	Not reported	Randomized, double-blind, placebo-controlled, parallel group, monocenter study	Urticaria symptoms and health-related quality of life improved significantly during omalizumab treatment compared with placebo.

AE, adverse event; CSU, chronic spontaneous urticaria; TPO, thyroperoxidase.

clinically meaningful changes in laboratory estimates or vital signs associated with omalizumab were observed. The other three RCTs were performed during the licensing program of omalizumab for CSU. The first published trial was a phase II dose-ranging study in which single doses of 75, 300, and 600 mg omalizumab were used [44]. Urticaria activity significantly decreased in the 300 and 600 mg treated patients when compared with the placebo group, but there was no difference between 75 mg and placebo. Notably, 600 mg omalizumab seemed to have a less pronounced (albeit not statistically significant) effect than 300 mg. Onset of action was detectable again as early as 1 week after administration and continued to improve throughout the trial. The rates of complete remission during treatment were 0% (placebo), 4% (75 mg), 36% (300 mg), and 29% (600 mg). The incidence of AEs was similar across treatment groups, and most were considered to not be related to the study drug. No serious AEs (SAEs) were observed during the treatment phase, and there were no reported observations of anaphylactic reactions or injection site reactions. The fourth and fifth RCTs were both phase III trials. In the study of Maurer *et al.* [43], omalizumab doses of 75, 150, 300 mg or placebo were administered in 4-week intervals for a period of 12 weeks followed by 12 weeks' follow-up. Urticaria symptoms and quality of life improved significantly in the 150 and 300 mg treatment group compared with placebo, but there was, again, no difference between 75 mg omalizumab and placebo. The largest decrease of symptoms was found in the 300 mg group. Percentages of patients with one or more AEs were similar across the treatment groups. Regarding SAEs, there were five in the 300 mg group, two in the placebo group, and one each in the 75 mg and 150 mg groups, with most SAEs in the 300 mg group reported during the follow-up phase. Again, no anaphylactic reactions were observed. Finally, the study of Kaplan *et al.* [42] compared omalizumab 300 mg and placebo administered in 4-week intervals over a total period of 24 weeks followed by 16 weeks' follow-up. Only patients who remained symptomatic despite treatment with H<sub>1</sub>-antihistamines at up to four times the licensed dose plus H<sub>2</sub>-antihistamines, leukotriene antagonists, or both qualified for inclusion. As in the previous RCTs, urticarial symptoms were found to strongly decrease during omalizumab therapy compared with placebo along with a significant quality-of-life improvement. Moreover, a significantly greater number of patients in the omalizumab group became completely symptom free (34%) compared with the placebo group (5%). Omalizumab was effective irrespective of the concomitant therapy of the patients used. During follow-up, the symptoms in patients returned to placebo values, which was also found by Maurer *et al.* [43], indicating that omalizumab is a symptomatic rather than a curative treatment.

In addition to these RCTs there are two small uncontrolled studies in patients with autoimmune CSU [45] or non-autoimmune CSU [46]. In the patients with autoimmune CSU [45] omalizumab was dosed according to the established asthma scheme, while the study in non-autoimmune CSU [46] applied 300 mg omalizumab in different intervals. Both studies found a strong reduction of urticaria symptoms during therapy. Also, the onset of action was found to be early after administration, as early as 48 h in some patients.

The RCTs and uncontrolled studies in CSU are complemented by numerous case series [47–60], some with more than 50 [56] or even 100 patients [53], and several case reports [61–67]. Taken together, these reports suggest that, in the case of complete remission of symptoms, CSU usually goes into remission on day 1 after the first injection and relapses within 2–8 weeks after the last

administration [56], that the majority of CSU patients on omalizumab are able to stop all concomitant CSU medications and remain asymptomatic treated with omalizumab alone [53], that omalizumab might be continued during pregnancy if inevitable [67], that maintenance of long-term remission is possible with omalizumab [63], and that omalizumab seems to be also effective in patients suffering from isolated angioedema [58]. In addition, there are case series [57, 68, 69] and case reports [70–78] available that have been performed in subjects with almost all inducible forms of chronic urticaria suggesting that omalizumab is also effective in many but not all individual patients [73, 77] with CIndU.

### Ciclosporin

A systematic review of ciclosporin in chronic urticaria is not available, but ciclosporin therapy in CSU was examined in three RCTs (Table 29.6) [79–81]. All of these studies were performed in adult patients unresponsive to antihistamines with starting doses of 4–5 mg/kg body weight daily. Two included only ASST-positive subjects [79, 80]. All three RCTs reported a significant improvement of patients during ciclosporin treatment. The proportion of patients showing marked improvement or full remission ranged from 42% to 50%. Notably, the onset of action of ciclosporin was found to be fast in most patients; that is, within 1 week after the initiation of treatment [79, 80]. Side effects were reported with variable frequency. In the study of Grattan *et al.*, 29 of 30 patients receiving ciclosporin reported side effects but these were not severe enough to require withdrawal [80]. Vena *et al.* [81] found AEs in 44 of 64 ciclosporin-treated subjects, of whom four discontinued therapy. In the study of Di Gioacchino *et al.* [79] ciclosporin was well tolerated with no dropouts related to relevant or irreversible side effects. However, the dose had to be reduced in three patients because of mild increases of serum creatinine levels, and four patients reported mild, transient side effects during the first 2 weeks of treatment.

In addition to these RCTs there are several uncontrolled studies [82–86] available in adult CSU patients only poorly responding to H<sub>1</sub>-antihistamines that also found good responder rates to ciclosporin therapy (between 30 and 100%). Four of these uncontrolled trials [82, 83, 85, 86] were performed with low doses of ciclosporin (3 mg/kg body weight or lower), thus suggesting that low-dose treatment may also be effective in CSU. This is particularly important when long-term ciclosporin treatment is considered. Regarding the side effect profile, the uncontrolled studies found comparable results to the RCTs. For ciclosporin therapy in children with CSU there is one case series available [87]. This demonstrates good efficacy and tolerability in seven children aged 9–16 years, with all showing a cessation of hives under a dose of 3 mg/kg body weight.

As in all other treatment options, the necessity for continued ciclosporin application should be reevaluated every 3–6 months [1]. There is no general recommendation on a maximum treatment duration in chronic urticaria, but the possible development of long-term side effects such as nephrotoxicity and increased risk for non-melanoma skin cancer need to be considered.

### H<sub>1</sub>-antihistamines plus leukotriene antagonists

A leukotriene antagonist may be added to H<sub>1</sub>-antihistamine treatment if monotherapy of the latter is not sufficient to control chronic urticaria symptoms. However, there is, as of yet, no systematic review on this approach, and the available evidence is inconclusive. Four RCTs have been performed in CSU [88–92] (Table 29.7) examining add-on therapy of leukotriene antagonists. Two of these

**Table 29.6** Ciclosporin treatment in chronic urticaria – available RCTs.

Author	Year	Disease examined	Sample size <i>n</i>	Age of patients	Treatment	Treatment duration	Study design	Main results
Vena <i>et al.</i> [81]	2006	CSU (unresponsive to regular dosed antihistamines)	99	Adults	Ciclosporin 5 mg/kg starting dose vs placebo (dose reduction after 2 and 4 weeks to 4 mg/kg and 3 mg/kg, co-treatment with cetirizine 10 mg)	16 or 8 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study	Urticaria symptoms and health-related quality of life improved significantly during treatment with ciclosporin compared with placebo. 60% of patients reported AEs with fewer patients in the placebo group. Elevated serum creatinine was the most commonly reported laboratory abnormality.
Di Gioacchino <i>et al.</i> [79]	2003	CSU (only ASST-positive patients with poor response to antihistamines requiring long-term corticosteroid treatment)	40	Adults	Ciclosporin 5 mg/kg starting dose vs cetirizine 10 mg (ciclosporin dose reduction after 8 weeks to 4 mg/kg)	16 weeks	Randomized, double-blind, controlled, parallel group, monocenter study	After 2 weeks the study had to be opened because of severe urticaria symptoms in 16 patients randomized to the cetirizine group. From that point all patients from the cetirizine group also received the ciclosporin regimen. At the end of 16 weeks' treatment, urticaria symptoms had improved significantly compared with baseline. 50% were in full remission during treatment. Onset of action usually occurred within 1 week. In 3 patients, the dose had to be reduced because of side effects.
Grattan <i>et al.</i> [80]	2000	CSU (only ASST-positive patients with poor response to antihistamines)	30	Adults	Ciclosporin 4 mg/kg starting dose vs placebo (dose reduction during the course of the treatment was performed based on tolerability, co-treatment with cetirizine)	4 weeks	Randomized, double-blind, placebo-controlled, parallel group, multicenter study (followed by an open-label extension)	Urticaria symptoms improved by >75% during treatment in 0% (placebo) vs 42% (ciclosporin) of patients. Onset of action occurred within 1 week. The overall response rate to randomized and/or open-label ciclosporin 65%. 29 of 30 patients receiving ciclosporin reported side-effects. These were not severe enough to require withdrawal.

CSU, chronic spontaneous urticaria; ASST, autologous serum skin test (test for autoreactive CSU); AE, adverse event.

trials were done in patients only poorly responding to H<sub>1</sub>-antihistamines [88, 90]. Di Lorenzo *et al.* [89] and Nettis *et al.* [91] each compared the effects of desloratadine 5 mg monotherapy and a combination of desloratadine 5 mg with montelukast 10 mg daily involving a total of 241 patients. Nettis *et al.* found the combination therapy to be significantly more effective than desloratadine monotherapy, whereas Di Lorenzo *et al.* [89] could not confirm this result. However, they were able to demonstrate that the combination therapy is superior to montelukast monotherapy. A third RCT in 95 subjects compared the effects of cetirizine 10 mg with the combination of zafirlukast 20 mg b.i.d. and cetirizine 10 mg [88] and found the combination to be significantly better in improving urticaria symptoms compared with cetirizine monotherapy. However, a subanalysis revealed that only those subjects with a positive ASST showed a significant benefit from the addition of zafirlukast to cetirizine. The fourth available small RCT looked at the effects of montelukast 10 mg or placebo as add-on to ongoing H<sub>1</sub>-antihistamine treatment. This study found no convincing evidence for an improvement of urticaria symptoms by the addition of montelukast.

In addition to the studies in CSU patients, two small RCTs [93, 94] were performed in 36 and 20 participants with delayed pressure urticaria. These trials showed significant superiority of the addition of montelukast 10 mg to either desloratadine 5 mg or loratadine 10 mg, when compared with monotherapy of the respective H<sub>1</sub>-antihistamine alone. In terms of the safety, none of the RCTs performed revealed any considerable side effects of the leukotriene-antagonist add-on treatment.

In addition to the above-mentioned studies, there are four RCTs [95–98] that examined monotherapy of leukotriene antagonists in CSU [95–97] or in a mixed population of CSU and CIndU [98]. Of the two studies comparing the efficacy of montelukast 10 mg with cetirizine 10 mg, one found superiority of montelukast in reducing urticaria symptoms [97], while in the other 8 of 10 patients had to discontinue montelukast treatment because their urticaria got worse [96]. Of the other two RCTs that both compared leukotriene antagonist therapy with placebo treatment, one found a beneficial effect of montelukast 10 mg on urticaria activity [95] while the other failed to demonstrate a therapeutic effect for zafirlukast 20 mg b.i.d. [98]. Finally, there are two uncontrolled studies that both point towards a beneficial effect of montelukast therapy in CSU [99, 100] and a case report showing efficacy of montelukast in a patient with cold urticaria [101].

### Drawbacks

First-generation H<sub>1</sub>-antihistamines are all sedating. Mistakenly, they are commonly regarded as safe by many laypersons and health-care professionals because of their long-standing use [102]. However, they reduce rapid-eye-movement sleep and impair learning and reduce work efficiency [102]. In addition, they are implicated in civil aviation, motor vehicle, and boating accidents, deaths as a result of accidental or intentional overdosing in infants and young children, and suicide in teenagers and adults [102]. Some exhibit cardiotoxicity in overdose [102].

Systemic steroids are highly effective in chronic urticaria but are characterized by an unfavorable side-effect profile when applied as



**Table 29.7** Leukotriene antagonist treatment in chronic urticaria – available randomized controlled trials on leukotriene antagonist add-on therapy.

Author	Year	Disease examined	Sample size <i>n</i>	Age of patients	Treatment	Treatment duration	Study design	Main results
Kosnik and Subic [90]	2011	CSU (poorly responding to antihistamines)	24	Adults	Add-on montelukast 10 mg vs add-on placebo to ongoing antihistamine treatment	2 weeks	Randomized, double-blind, placebo-controlled, crossover, monocenter study	No clear improvement of urticaria symptoms occurred during montelukast add-on treatment compared with placebo. A subanalysis suggested the possible existence of mild effects only in the most severely affected patients.
Wan [92]	2009	CSU	120	Adults	Hydroxyzine 25 mg plus cetirizine 5 mg b.i.d. vs hydroxyzine 25 mg plus famotidine 20 mg b.i.d. vs hydroxyzine 25 mg plus montelukast 5 mg b.i.d. vs placebo b.i.d.	4 weeks	Randomized, single-blind, placebo-controlled, parallel group, monocenter study	An improvement of urticaria symptoms of at least 25% occurred in 53% of patients during hydroxyzine plus montelukast treatment compared with 0% in the placebo group, 23% in the hydroxyzine plus cetirizine group, and 63% in the hydroxyzine plus famotidine group. Mild to moderate sedation occurred in 6 patients of the hydroxyzine plus montelukast group, in 6 patients of the hydroxyzine plus famotidine group, and in 8 patients of the hydroxyzine plus cetirizine group.
Nettis <i>et al.</i> [93]	2006	DPU	36	Adults	Desloratadine 5 mg vs desloratadine 5 mg plus montelukast 10 mg vs placebo	2 weeks	Randomized, double-blind, placebo-controlled, parallel group, monocenter study	The DPU challenge test reaction as well as the clinical DPU symptoms were reduced significantly by desloratadine monotherapy and the combination with montelukast compared with placebo. Add-on of montelukast to desloratadine reduced both outcomes significantly stronger as compared to desloratadine monotherapy. Complete remission was achieved in 0% (placebo), 27% (desloratadine 5 mg), and 83% (desloratadine plus montelukast). No side effects occurred throughout the study.
Di Lorenzo <i>et al.</i> [89]	2004	CSU	160	Adults	Desloratadine 5 mg vs montelukast 10 mg vs desloratadine 5 mg plus montelukast 10 mg vs placebo	6 weeks	Randomized, double-blind, placebo-controlled, parallel group, two-centre study	No improvement of urticaria symptoms occurred during desloratadine plus montelukast treatment compared with desloratadine monotherapy. Both groups were significantly more efficacious compared with placebo and with montelukast monotherapy. A low incidence of AEs was observed in the study. All AEs were rated as mild.
Bagenstose <i>et al.</i> [88]	2004	CSU (poorly responding to antihistamines)	95	12 years and older	Cetirizine 10 mg vs cetirizine 10 mg plus zafirlukast 20 mg b.i.d.	3 weeks	Randomized, double-blind, placebo-controlled, parallel group multicenter study	Urticaria symptoms improved significantly better during zafirlukast add-on treatment compared with cetirizine monotherapy. In a subanalysis, only those subjects with a positive ASST showed a significant benefit from the addition of zafirlukast to cetirizine. No significant AEs occurred throughout the study.
Nettis <i>et al.</i> [91]	2004	CSU	81	15 years and older	Desloratadine 5 mg vs desloratadine 5 mg plus montelukast 10 mg vs placebo	6 weeks	Randomized, double-blind, placebo-controlled, parallel group, monocenter study	Urticaria symptoms improved significantly during desloratadine monotherapy and the combination of desloratadine with montelukast compared with placebo. The montelukast add-on therapy was significantly more efficacious compared with desloratadine monotherapy. No side effects occurred throughout the study.
Nettis <i>et al.</i> [94]	2003	DPU <sup>2</sup>	20	adults	Loratadine 10 mg vs loratadine 10 mg plus montelukast 10 mg	2 weeks	Randomized, double-blind, controlled, parallel group, monocenter study	The DPU challenge test reaction was completely suppressed (complete remission) during treatment in 80% (loratadine plus montelukast) and 20% (loratadine monotherapy). 20% of patients treated with montelukast plus loratadine reported somnolence.

CSU, chronic spontaneous urticaria; DPU, delayed pressure urticaria; AE, adverse event; ASST, autologous serum skin test (test for autoreactive CSU).

long-term treatment. Therefore, corticosteroids should only be used short term, for acute exacerbations. Since there are adequate alternative treatments available, steroid administration can usually be avoided.

Ciclosporin has been found to be effective in chronic urticaria, but it is well established that side effects such as hypertension, hypertrichosis, elevation of creatinine levels up to renal insufficiency, and dyslipidemia may occur. Patients intended for ciclosporin should, therefore, be selected carefully, as well as examined and monitored accurately before and during treatment. If this is done, ciclosporin is usually well tolerated. In most patients, low to medium doses are sufficient.

In addition, to the guideline-recommended treatments, there are a lot of additional therapies that have been reported to work in chronic urticaria (e.g., dapsone, H<sub>2</sub>-antihistamines, sulfasalazine, methotrexate, and phototherapy) but only have very limited or inconsistent evidence. For further details, please see Zuberbier *et al.* [1]. These options should only be used if all recommended first- to third-line therapies are not sufficient to control the patient's symptoms or are contraindicated or not available. Moreover, such widespread treatment failure should prompt a reevaluation of the urticaria diagnosis. In particular, urticaria vasculitis and autoimmune-inflammatory conditions should be clearly ruled out. On the other hand, some treatment alternatives formerly proposed for chronic urticaria have been shown to be ineffective in double-blind, controlled studies and should no longer be used in the average patient [1]. These include tranexamic acid and sodium cromoglycate in CSU, nifedipine in symptomatic dermographism, and colchicine and indometacin in delayed pressure urticaria [1].

### Comment

The guideline-described treatment algorithm includes all reliable drugs for patients with chronic urticaria; that is, H<sub>1</sub>-antihistamines, omalizumab, ciclosporin, and montelukast. This armory is sufficient to treat the vast majority of patients. All other treatment options can usually be avoided, which will help to obtain a timely improvement of urticaria symptoms in most patients but also to prevent frustration on both the patient's and the physician's side.

### Implications for clinical practice

Chronic urticaria is one of the most frequent skin diseases, commonly associated with a major impairment of the patient's quality of life. The first step in the management should be the correct diagnosis and classification, since the further proceeding strongly depends on the subtype present. In CSU, a search for underlying causes is advisable in patients with long-standing and/or severe disease based on clues from the patient's individual history. In all others, only a basic laboratory is recommended to rule out severe systemic disease. In CIndU, underlying causes are unknown for most subforms. Further diagnosis here mainly aims at the identification of triggers and the determination of trigger thresholds, because the latter allow for assessing disease status and response to treatment.

Whenever possible, chronic urticaria patients should be treated causally. For all other cases, the current guidelines suggest a symptomatic treatment algorithm that does not distinguish between different subforms. The first-line therapies are second-generation H<sub>1</sub>-antihistamines in licensed doses, followed by an up dosing up to fourfold as a second-line option. H<sub>1</sub>-antihistamine therapy is safe and usually well tolerated, if first-generation drugs with sedative side effects are avoided. A continuous dosing schedule should be

preferred over on-demand treatment. Since there is a considerable proportion of patients who not respond sufficiently to H<sub>1</sub>-antihistamines, regardless of which dose is applied, an add-on of omalizumab, ciclosporin, or montelukast may be performed as a third-line treatment. The best evidence is currently available for omalizumab, which has been first licensed in 2014 for the treatment of CSU, where it is highly effective, safe and well tolerated, and has a fast onset of action. In contrast to asthma, the dosing scheme is not dependent on total IgE levels and body weight. Instead, doses of 150 or 300 mg per administration are usually sufficient to achieve good responses. Ciclosporin has also been repeatedly shown to exhibit good efficacy in CSU. However, not all patients qualify for this treatment since several potential side effects and contraindications have to be considered. Consequently, patients have to be carefully selected and monitored. Montelukast has the weakest evidence for efficacy of all third-line therapies, but is characterized by a good safety profile. Systemic corticosteroids may also be used, but only in short courses for acute exacerbations. A long-term treatment with systemic corticosteroids is strongly advised against because of the unfavorable long-term side-effect profile. Since all subtypes of chronic urticaria show spontaneous remission, the need for treatment should be reviewed every 3–6 months.

### Key points

- Chronic urticaria is a common disorder that significantly impairs the patient's quality of life.
- A correct diagnosis and classification of chronic urticaria is important since the management depends on the subtype present, and important differential diagnosis should be excluded.
- In CSU, a search for underlying causes is justified in patients with long-standing and/or severe disease.
- Possible causes of CSU include autoreactivity, autoallergy, chronic infections, and food intolerance.
- In CIndU, underlying causes are unknown for most subforms.
- Diagnosis in CIndU mainly aims at the identification of triggers and the determination of trigger thresholds.
- A causal treatment of chronic urticaria should be performed whenever possible; all remaining patients should be treated symptomatically.
- The aim of symptomatic treatment is complete symptom control.
- A symptomatic treatment algorithm is recommended by the current guidelines; this does not distinguish between different chronic urticaria subforms.
- The first-line symptomatic therapy is second-generation H<sub>1</sub>-antihistamines in licensed dose, followed by an up dosing up to fourfold as a second-line option.
- Third-line treatment options comprise add-on omalizumab, ciclosporin, or montelukast.
- Of the third-line options, omalizumab has currently the best available evidence.
- First-generation, sedating H<sub>1</sub>-antihistamine should not be used, owing to their unfavorable side-effect profile.
- Systemic corticosteroids should only be applied in short courses to manage acute exacerbations.
- All subtypes of chronic urticaria show spontaneous remission. Therefore, the need for treatment should be reviewed regularly every 3–6 months.
- Disease activity, disease control, and impact of chronic urticaria should be examined and/or followed with validated patient-reported instruments, such as the urticaria activity score, angioedema activity score, urticaria control test, chronic urticaria quality of life questionnaire and angioedema quality of life questionnaire.

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## SECTION 2 Skin cancer, moles, and actinic keratoses

Robert Dellavalle, editor

### CHAPTER 30

## Primary prevention of skin cancer

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### Background

#### Incidence, mortality, and morbidity of skin cancers

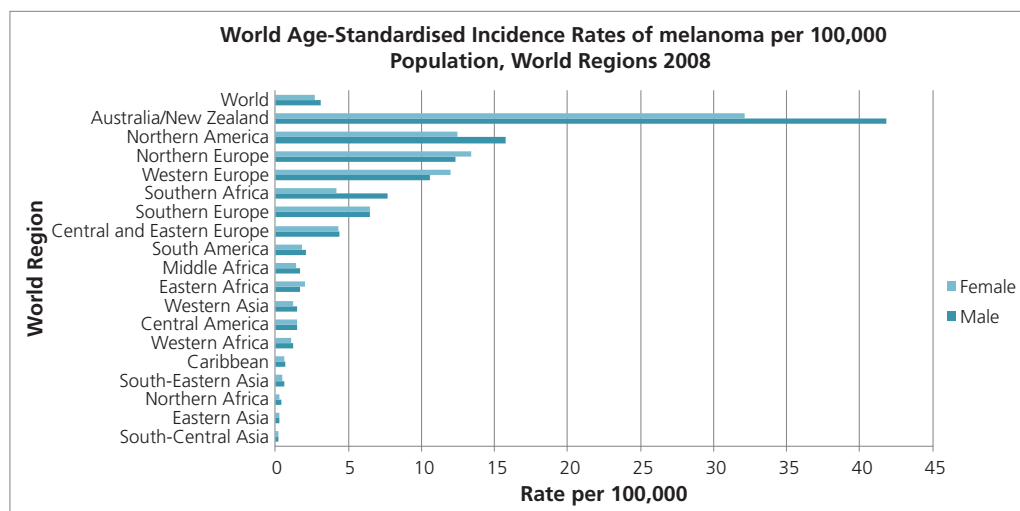
Skin cancer is more common than any other type of cancer in white populations, and keratinocyte (KC) cancers are by far the most common, comprising mainly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

BCC and SCC incidence rates are high, around 800/100 000 and 330/100 000 respectively in sunny countries like Australia and lower in temperate climates such as the UK, with rates of around 60/100 000 and 30/100 000 respectively. Incidence of BCC rises with age, but lesions frequently occur in adults before age 50 [1] and are seen on the trunk as well as on the face [2]. SCC is diagnosed predominantly in adults over 60 years on the head and forearms. In the USA in 2006 it was estimated that a total of 2 152 500 people were treated for some 3 507 700 KC cancers [3]. These figures show also that repeated occurrences of primary KC skin cancer are frequent in affected patients. Men usually have

higher incidence rates than women overall, but this can vary by age group, and differences are ultimately thought to reflect sex-specific differences in sun exposure. Though BCCs and SCCs respond well to treatment and have relatively low mortality rates, their high incidence rates mean that their associated health-care costs impose a substantial financial burden on health-care systems [4].

Melanoma is the third commonest but most serious form of skin cancer, with incidence rates varying widely across the globe (Figure 30.1). Melanoma incidence in white Caucasians is around 50/100 000 in Australia compared with around 10/100 000 in the UK, and corresponding mortality rates are 5.7/100 000 and 2.6/100 000 respectively.

While widespread increases in melanoma incidence have been noted in white populations worldwide in the last two to three decades, much of the increase has been ascribed to increased detection of nonfatal melanomas rather than to a true rise in incidence of the disease, since the corresponding melanoma mortality rates have hardly changed over the same period [5].



**Figure 30.1** World age-standardised incidence rates of melanoma per 100 000 population, world regions 2008. Source: Ferlay *et al.* [85]. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010. Available from: <http://globocan.iarc.fr>. Reproduced with permission of the IARC.

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## Risk factors

### Pigmentation phenotype

Skin cancer is mostly a disease of white-skinned populations [6]; among those of European ancestry, skin cancer incidence is higher among those who have lighter complexions with light hair and eye color, freckling, and a susceptibility to sunburn [7]. In addition, the presence of atypical nevi or having large numbers of common acquired melanocytic nevi raises the risk of melanoma [8,9]. Although the majority of melanomas arise *de novo*, both common and atypical nevi can act as precursors, and around 20–40% of melanomas have histological evidence of a contiguous nevus [10].

### Genetic susceptibility

Xeroderma pigmentosum (XP) patients have an extreme photosensitivity to ultraviolet (UV) radiation as the result of a deficiency in the enzyme for excision repair of UV-damaged DNA and are highly susceptible to all three types of skin cancer. Similarly, variants of the melanocortin-1 receptor (MC1R) gene, indicated by red hair and lack of tanning ability, are associated with increased risk of all types of skin cancer.

Patients affected by Gorlin's syndrome (nevoid basal cell carcinoma syndrome) carry mutations in the *patched* gene, a tumor suppressor gene, and they develop multiple BCCs from an early age [11]. Up to 90% of sporadic BCCs also show *patched* mutations [12]; the *patched* gene product is part of the sonic hedgehog (Shh) protein receptor. It is thought that upregulation of the Shh pathway is the pivotal abnormality in BCCs and little more than Shh upregulation may be needed for BCC carcinogenesis [13]. Family linkage studies have identified three major melanoma susceptibility genes: CDKN2A, ARAF, and CDK4 [14], though of all melanomas newly diagnosed, familial melanoma accounts for fewer than 10%.

### Exposure to the sun and ultraviolet radiation

Epidemiological studies consistently show that white populations who receive low sun exposure rarely develop skin cancer [15,16]. Further evidence of the predominant causal role of solar UV radiation in development of all three types of skin cancer is their consistent association with clinical signs of chronic sun damage [17,18], notwithstanding an overall lack of association with self-reported chronic sun exposure [19,20]. This may be partly due to self-selection of indoor work by sun-sensitive people [20].

The majority of sporadic SCCs carry mutations of the *p53* tumor-suppressor gene [21], with "UV-signature mutations" showing they were caused by exposure to UV radiation. The relationships between sun exposure and BCC and melanoma are complex, however, and interpretation of analytic study findings is frustrated by the difficulty in measuring life-course sun exposure and by the knowledge that sun-related behavior and the biological effects of sun exposure are both highly modified by host factors.

In addition to solar UV, exposure to artificial sources of UV radiation also increases skin cancer risk. The use of tanning devices is associated with a significant increase in BCC [22], SCC, and melanoma occurrence [23], especially with young age at first use. Long-term exposure to phototherapy of oral methoxypsoralen (psoralen) and UV A radiation for psoriasis and other skin conditions has also been shown to increase the risk of developing melanoma [24].

### Early diagnosis

Early diagnosis is the key to reducing deaths from skin cancers in the short term, especially melanoma, as delayed diagnosis increases the risk of mortality. Survival rates have improved greatly in the last

few decades mainly because doctor and patient awareness have increased so that today the majority of melanoma patients are diagnosed with thin melanomas ( $\leq 1.00$  mm) and have an overall 20-year survival rate of 96% [25].

### Aims in primary prevention

Primary prevention involves interventions designed to prevent skin cancer from occurring for the first time. Interventions for primary sun protection aim to change risk behavior (as an intermediate measure) in order to reduce the incidence of skin cancer (as a health outcome measure). The main sun-protection strategies are use of sunscreens, wearing of wide-brimmed hats and clothing cover when outdoors, staying out of the sun between 10 a.m. and 4 p.m., and use of shade. Other interventional approaches to direct primary prevention of skin cancer have been based on chemoprevention.

### Search strategy

Studies included in this chapter were found by searching the Cochrane Library and PubMed. Searches were conducted in May and June 2012. The MESH headings used were Skin Neoplasms/prevention & control\* and Melanoma/prevention & control\*, restricted to reviews, meta-analyses, randomized or controlled clinical trials, and those published in the last 5 years. Where a continuous update was provided for any of the reviews, the latest update was used. While the available reviews used different grading systems for the strength of the evidence, none utilized the strength of recommendations taxonomy (SORT) [26], which we applied to the findings as summarized in Table 30.1, and the findings of the reviews have thus been transferred into SORT measures.

For brevity, where evidence from reviews was available it was used, before randomized trials were sought and summarized.

## Review of evidence on primary prevention

### Behavioral interventions to reduce skin cancer incidence

Clinicians can play an important role in primary prevention of skin cancer. Given the plethora of information now available, patients value clinicians' advice and help to integrate their preferences with the best available evidence [27]. Consultations provide opportunities to support patients' decision-making and to discuss cues for action [28]. While the link between sun exposure behavior and skin cancer incidence is well established, for the vast majority of behavioral interventions evidence is available only for intermediate outcomes such as sunburn or tanning rather than skin cancer incidence or mortality, owing to the long latency of skin cancer development. As exemplified by the model guiding the review of the literature performed by the Community Preventive Services Task Force [29], it is expected that improvements in these intermediate outcomes (i.e., reduction in sunburn, increase in clothing cover, etc.) will lead to better patient outcomes measured by quality of life, incidence, or mortality. Behavioral primary prevention interventions aim to improve personal protection from UV through:

- covering the skin with clothing, hats, or sunscreen for areas of the skin that are not covered by clothing (Figure 30.2);
- protecting the skin around the eyes (and the eyes) with sunglasses;
- staying in shade provided by natural or artificial sources; and
- avoiding sun exposure, especially during peak UV hours.

Kasparian *et al.* [30] summarized the prevalence of current use of these methods, ranging from 4 to 86% for hat, 4 to 70% for cloth-

**Table 30.1** Summary of evidence-based reviews of behavioral interventions.

	Children/parents	Adolescents	Adults	Special groups (e.g., high-risk persons, outdoor workers)
Self-education, education, health professional counseling	SORT A USPSTF-B  Community Preventive Services Task Force: evidence insufficient for childcare centers, and secondary school setting, but sufficient in primary school settings for improved covering up behaviors NICE recommendation 1+4: health professionals to deliver low-cost education and tailored preventive messages	SORT A USPSTF-B	SORT B USPSTF-I	SORT B Community Preventive Services Task Force: sufficient evidence that interventions increase sun protective clothing in tourism settings Appearance-based intervention effective for outdoor workers [50] In beachgoers, education plus UV photo reduced sunburn and increased use of protection [49]
Policy/community mobilization	SORT B NICE recommendation 5: schools and other providers of outdoor activities develop and implement policies to protect children and adolescents  Community Preventive Services Task Force: evidence insufficient for childcare centers, and secondary school setting, but sufficient in primary school settings for improved covering up behaviors		Community Preventive Services Task Force: sufficient evidence that interventions increase sun protective clothing in tourism settings	SORT B NICE recommendation 2: target high-risk groups NICE Recommendation 5: develop and implement policies to protect outdoor workers
Media/social media	SORT B/NICE recommendation 1: continue to deliver low-cost local and national mass media skin cancer prevention campaigns			
Multicomponent	SORT B/NICE recommendation 1: integrate education with other health promotion activities and mass media Improvements in protection and reduction in body area exposed following multimedia campaign in Victoria [53] Reduction in skin cancer incidence in Victoria [61]			

SORT, Strength of Recommendations Taxonomy; USPSTF, US Preventive Services Tasks Force; NICE, National Institute for Health and Excellence, UK.



**Figure 30.2** Sun protective clothing, hats, sunglasses and sunscreen are common skin cancer primary prevention methods (reproduced with permission from Queensland Health, 2012).

ing, 16 to 62% for sunglasses use, and 15 to 59% for seeking shade. Sun protection by sunscreen use, reported by 7–90% of people, is complicated by dependence on application thickness, with most people applying about 1 mg/cm<sup>2</sup> providing a sun protection factor (SPF) of about one-third of the sunscreen's advertised SPF [31].

As summarized by the UK National Institute for Health and Clinical Excellence (NICE) guidelines (number 6) [32], behavioral interventions can be delivered through a number of means, including education, counseling by a health-care provider, policy or environmental changes, community-wide engagement through media or social media campaigns, or the simultaneous use of several of these components. For any of these methods, behavioral interventions should follow a set of best-practise rules, including:

- being based on a thorough needs assessment of the target population;

- taking account of existing strength and barriers within the target population;
- applying the latest evidence for effective behavior change;
- being delivered by trained personnel; and
- featuring an evaluation of their effectiveness [32].

Increasingly, intervention programs are guided by health behavior theories, such as the health belief model [33], social cognitive model [34], the preventive health model [35], the theory of planned behavior [36], or the transtheoretical model [37,38]. While these health behavior theories have allowed the development of effective interventions to change peoples' knowledge, attitudes, and intentions, they often fail to similarly influence automatic, affective systems driven by situational factors and social norms [39]. For example, despite knowing that excessive sun exposure is unhealthy, adolescents' fashion norms often lead to deliberate tanning [40]. Modern interventions thus integrate components that specifically target social and motivational barriers [41]. UV photographs highlight solar damage to the skin and skin aging caused by tanning, and so they can provide visual cues to facilitate behavior change [42].

In addition to intervening at the individual level, meso- and macro-level changes to community, national or international appearance norms are also needed before skin cancer prevention is regarded as normative behavior [43].

There are 17 evidence-based programs related to skin cancer primary prevention that are currently listed on the USA National Cancer Institute's research-tested intervention programs website [44], and cancer agencies around the world have developed comprehensive programs such as SunSmart (Australia and UK) and SunWise (USA). In 2004, a systematic review of interventions to reduce skin cancer was published by the Community Preventive Services Task Force [29], which also integrated previous reviews by other agencies (IARC, US Preventive Services Tasks Force (USPSTF), and the US Centers for Disease Control and Prevention).

More recently, a systematic for the USPSTF review has summarized the evidence focusing on behavioral counseling [45,46], and five systematic reviews have been undertaken for NICE. Each of these reviews posed different research questions: the Community Preventive Services Task Force was guided by a conceptual framework for pathways from knowledge, attitudes to behavior change to decrease in skin cancer; the USPSTF review was designed to answer five behavioral counseling-focused questions; while the NICE reviews were guided by a set of broad research questions. An Australian review has provided a comprehensive summary of available evidence since 1980 [30]. One review has focused solely on interventions for outdoor workers [47].

### Interventions directed at individuals

All reviews concurred that educational or behavioral interventions directed at individuals are effective in improving sun protective behaviors, including those directed at parents of newborn children, primary school children, adolescents, and young adults. Recent interventions have commonly included individualized or tailored feedback and appearance-based components such as UV photographs targeting the affective system [29,45,46]. For example, the USPSTF review recommended that behavioral counseling for children, adolescents, and young adults who have fair skin is effective (USPSTF-B – indicating that the USPSTF recommends the services as there is high certainty of moderate net benefit or moderate certainty of moderate to substantial benefit [45]). Similarly, NICE guidelines recommend behavioral counseling of these groups [48] (Table 30.1). With regard to adults, the USPSTF states that the evidence is insufficient to make recommendations either for or against behavioral counseling even though several randomized trials have involved adults. These trials have mostly focused on high-risk groups for either occupational, recreational, or family risk reasons (e.g., beachgoers [49], outdoor workers [50], or relatives of patients with skin cancers [51]). In Manne *et al.*'s study [51], a tailored compared with a generic print and telephone counseling intervention significantly improved sun protection habits among first-degree relatives of patients with melanoma. UV photographs in combination with a cancer-specific or aging-specific video compared with control were effective in increasing sun protection behavior and reducing skin tanning in a high-risk population of outdoor workers [50]. Falk and Anderson [52] randomized adults to a personalized doctor's consultation or a doctor's consultation plus a test of sun sensitivity compared with educational letter-only control. Both groups receiving the doctor's consultation reduced their sun exposure behavior significantly more than the group who received written education only. However, in average-risk individuals the difference in sun protection that can be achieved between groups may be less than in high-risk groups, making statistically significant improvements which could then result in recommendations by agencies less likely.

### Comment

Education and counseling are the cornerstones of health promotion and have been found to be effective in improving intermediate skin cancer prevention outcomes.

### Policy interventions and community mobilization

Policy and environmental interventions aim to promote sun-safe practices by setting standards for expected relevant behaviors and providing the necessary education, supportive structures, and physical means to achieve high sun protection or reduced sun exposure

behaviors. Such interventions have been tested in childcare, school, outdoor worker, and community settings and have been found to be effective in at least some of these settings. The majority of trials have been conducted in primary school settings, and have showed significant improvements of at least 25% in children's sun-protective clothing [29]. The provision of sun-protective policy interventions in outdoor workers was found to increase the prevalence of wearing sun-protective clothing by 11% across several randomized trials [29]. The provision of shade within intervention high schools in Australia resulted in significantly greater use of shade by adolescents compared with shade use in other schools in a cluster randomized trial [53].

Policies are commonly more effective when they are developed together with the community or organizations that must follow the policy [48]. Some policy interventions, such as providing personal protective equipment or shade, can be costly, and NICE therefore only recommends adding shade to new buildings rather than improving existing facilities. NICE recommendations regarding policy interventions have focused on schools and outdoor activity providers as well as high-risk workers (Table 30.1). In addition to implementing the policies that fit with the culture of the community or organization, regular review of the environmental structures, policy documents, and enforcement of policy-compliant behaviors is needed to ascertain continued relevance [54].

### Comment

Policies are useful to set clear and tangible goals and outcome expectations, but to be effective they need to be acceptable to the target audience, supported by key stakeholders, and regularly reviewed for their currency.

### Interventions using media or social media

In the review by the Community Preventive Task Force, 12 reports were identified, but only two measured behavioral outcomes, with neither providing sufficient evidence for the effectiveness of media campaigns alone [29]. As described by Kemp *et al.* [55], mass media can be a valuable component of health behavior communication programs, but consistency of message and competing market forces may limit their reach or intended purpose. The NICE guidelines recommend that health practitioners use low-cost local media campaigns to raise awareness of skin cancer prevention [48]. They also detail recommendations on optimizing (recommendation 3) and tailoring (recommendation 4) message content, including personal and environmental risk assessment. They mention the whole range of options for sun protection and discuss the balance between risks and benefits of sun exposure [48].

### Comment

Few interventions have relied solely on media or social media, and media intervention components are most likely to be integrated into multicomponent interventions as reviewed below.

### Multicomponent interventions

The majority of skin cancer prevention interventions use some combination of education strategies, mass-media campaigns, and environmental policy changes. They usually have a logo and name, a theme, a specific set of messages, and focus on clearly defined geographic areas with specific targets. The Community Task Force Review included studies that had clearly defined geographic boundaries and at least two components in two settings [29]. Comprehensive community-wide interventions are multiple-level



approaches that address large numbers in the given population. Examples include the 20-year “Slip! Slop! Slap!” and SunSmart campaigns in Victoria, Australia [56], and by Cancer Research UK, Sun Pass in Germany [57], the SunSafe project in New Hampshire [58], and the Falmouth Safe Skin Project in Massachusetts [59]. Australia has had the longest-running and most sustained campaigns, and there are indications of slowing skin cancer incidence rates among people over 60 years and a drop in incidence of under 60 years in Victoria, the state with the most sustained investment into SunSmart [60,61].

### Comment

While evidence for a decrease in incidence of melanoma is accumulating, the changes in incidence may take longer to become apparent in populations with lower baseline incidence rates.

### Barriers to sun protection, and risks and harms of promoting sun protection

For the NICE guidelines, two reviews of qualitative research studies specifically summarized barriers to sun protection that need to be overcome in the future [48]. The most prominent ones included perceptions of skin cancer being less serious and more easily treated than other cancers (evidence statement 5.8), perceptions of tanned skin being desirable (evidence statement 5.13), and being indicative of good health (evidence statement 5.15). Specific barriers to each of the sun protection methods were also identified, including cost concerns, allergic or unpleasant skin reaction to sunscreen, and uncomfortable or unfashionable sun protective clothing. Barriers to sun protection in various settings have also been described by NICE [48] and Kasparian *et al.* [30]; for example, child-care workers raised concerns about whether applying sunscreen to children formed part of their roles and responsibilities.

With regard to potential for harm through sun protection, the USPSTF assessed but could find no evidence that counseling about sun protection leads to reduction in physical activity in children [45]. The NICE guidelines considered reductions of physical activity and vitamin D production as potential harms of sun protection [48]. Recent results from the Nambour trial, however, showed no difference in vitamin D levels between participants assigned to daily sunscreen or usual care, and also no difference depending on whether or not participants reported use of various sun protection methods [62]. The only exception was participants who usually or almost always stayed in the shade: on average they had a mean vitamin D level two points below those not usually seeking shade [62].

### Health-economic modeling and evaluation

The NICE report undertook hypothetical economic modeling of three potential interventions. A home-based intervention directed at parents and children provided the most cost-effective intervention with an estimated £6700 per quality adjusted life years (QALY), while interventions directed at school children or young adults and adding shade structures to new buildings resulted in cost per QALY of £20 000–30 000. Estimates were also provided for a mass-media campaign costing £0.0028–0.0093 per person to be cost-effective for increasing the proportion of people using sunscreen by 2–6.6% [48]. Kyle *et al.* [63] provided cost-effectiveness calculations for the US SunWise program and concluded that every dollar invested had the potential to save between \$2 and \$4 in medical and productivity loss costs. Cost-effectiveness analysis of the SunSmart campaign in Victoria, Australia, estimated that based on the change in skin

cancer incidence in Victoria an intensive SunSmart campaign would likely be cost-effective, and prevent more than 100 000 disability adjusted life-years over a period of 20 years [64].

### Preventive interventions with skin cancer as the primary outcome

Several trials of chemoprevention of skin cancer have assessed occurrence of new BCC, SCC, or melanoma as direct outcomes.

#### Sunscreen

Sunscreen application to exposed skin is the most common means of self-protection from the sun in order to reduce acute and/or long-term skin damage. A single community-based skin cancer prevention trial has been conducted in the township of Nambour, Australia [65]. The Nambour Skin Cancer Prevention Trial evaluated daily sunscreen use (together with betacarotene supplementation) in the prevention of BCC and SCC. At the end of the trial, in comparison with people randomized to using sunscreen at their discretion, including nonuse, people randomized to daily use of a broad-spectrum SPF 15+ sunscreen had no reduction in BCC but a 40% reduction in SCC tumors [66], which was maintained 8 years later [67]. Rate of acquisition of actinic keratoses (AKs) was also reduced in the daily sunscreen group [68], as was the time to subsequent BCCs after the first BCC [69] in the trial period, though this finding could have been due to chance. Nambour Trial participants were followed up 10 years after trial cessation for melanoma occurrence. Those allocated to daily sunscreen use showed a 50% reduction in all primary melanomas (at a borderline level of statistical significance), including a substantial reduction in invasive melanomas, compared with controls [70]. This evidence is consistent with findings from a randomized controlled trial among Canadian children allocated to sunscreen application for 2 years who showed a small reduction in new melanocytic nevi compared with controls, especially among children with freckles [71].

### Can other chemoprevention interventions reduce the risk of cancer?

A large proportion of chemoprevention trials have been conducted in subpopulations at unusually high risk of skin cancer because of genetic disorders or immunosuppressive therapy. Since findings regarding preventive efficacy do not concern primary prevention measures that can be applied to the majority of patients at risk of skin cancer, evidence from such trials has not been included here.

#### Micronutrients

In the 1990s, the International Agency for Research on Cancer reported on two separate meta-analyses of vitamin A intake [72] and carotenoids [73] and their effect on cancers, including skin cancer, and concluded that there was no association between either micronutrient and skin cancer. In 2009, a systematic review and meta-analysis of randomized controlled trials reviewed the effect of betacarotene supplementation on cancer incidence, including skin cancers [74], and showed no association with BCC, SCC, or melanoma among the five relevant trials. Similarly, a Cochrane review that reported on two randomized controlled trials that evaluated the efficacy of selenium supplementation for KC cancer prevention found no protective efficacy against nonmelanoma skin cancer [75]. The effects of 400 IU of vitamin D3 combined with 1000 mg of calcium supplementation on skin cancer were assessed post hoc in the Women's Health Initiative randomized placebo-controlled trial among 36 282 postmenopausal women aged 50–79

with 7 years mean follow-up. Only aggregate self-reported KC outcomes were available, but no differences were seen between treatment groups; nor was there any difference in melanoma rates overall, though subgroup analyses in women with history of KC assigned to the vitamin D plus calcium treatment versus placebo had a reduced risk of melanoma not seen in women without a past history of KC.

#### Comment

The evidence from randomized controlled trials suggests that vitamin A, betacarotene, selenium in brewer's yeast tablets, and relatively low-dose vitamin D supplementation plus calcium are not effective in preventing skin cancers.

#### Systemic retinoids

In a past meta-analysis of retinoids and cancer prevention, including skin cancer, the International Agency for Research on Cancer concluded that, despite some agents showing cancer preventive activity in humans, their toxicity was likely to limit their use [76]. Twelve years later this remains the case, with therapeutic use reserved usually for very high-risk patients actively developing large numbers of new skin cancers, such as those with XP, nevoid BCC syndrome, or selected transplant patients [77,78]. A single randomized controlled trial has assessed the efficacy of 25 mg oral acitretin, 5 days a week for 2 years as a skin cancer chemopreventive agent versus placebo treatment in 70 immunocompetent high-risk patients (two or more KCs in the previous 5 years) [79]. There was a nonsignificant 60% reduction in the rate of new primary BCCs and SCCs combined, but the authors reported that the results, while negative, appeared to suggest that acitretin decreased the total number of BCCs and SCCs similarly, though with significantly more mucositis and skin toxicities compared with placebo [79]. There is the possibility, however, given the extensive ongoing research into systemic retinoids, that novel retinoids with improved bioavailability and less toxicity will be developed [78] with the result that in the future they may be added to the clinician's armamentarium for general skin cancer chemoprevention.

#### Topical retinoids

Tretinoin applied topically avoids the systemic side effects of oral retinoids and was evaluated in 1131 US Veterans with two or more previous KCs on the face or ears in the prior 5 years [77]. Patients randomized to topical 0.1% tretinoin or a matching vehicle control for 1.5–5.5 years showed no difference in time to development of new BCC or SCC on the face or ears.

#### Comment

Evidence does not support the use of retinoids to prevent skin cancers in the general patient population.

#### Can other medicines reduce the risk of skin cancer?

A meta-analysis of randomized controlled trials of statins for reducing cardiovascular outcomes was conducted in 2009 to evaluate possible chemopreventive potential against melanoma through anti-inflammatory, immunomodulatory, or antiangiogenesis mechanisms [80]. Based on 16 randomized controlled trials involving 62 568 patients (mean age 60 years, average follow-up 4.7 years), statin use did not significantly affect the risk of melanoma.

The possible preventive effect of aspirin and other nonsteroidal anti-inflammatory drugs on the development of various types of

skin cancer as exploratory outcomes has been studied in two trials. A double-blind placebo-controlled randomized trial across eight US academic medical centers evaluated 200 mg celecoxib, a cyclooxygenase 2 inhibitor, or placebo twice daily for 9 months in 240 patients each with 10–40 AKs at baseline [81]. Numbers of BCCs (relative risk [RR], 0.40; 95% confidence interval [CI], 0.18–0.93;  $P = 0.032$ ) and SCCs (RR, 0.42; 95% CI, 0.19–0.93;  $P = 0.032$ ) were fewer in the celecoxib arm, though incidence of AKs, the primary outcome measure, showed no difference compared with placebo. Serious adverse events were similar in the two arms. In the Women's Health Study, a randomized trial of aspirin and vitamin E enrolled 39 876 US women aged 45 or more. Women were randomized to receive either 100 mg aspirin or aspirin placebo every second day and followed up for an average of 10 years for newly diagnosed invasive cancer at all sites, except for KC [82]. No difference in the incidence of melanoma (RR, 0.97; 95% CI, 0.70–1.36) was seen in the low-dose aspirin compared with the placebo group.

#### Comment

Celecoxib may prevent SCCs and BCCs in patients with sun-damaged skin who have high numbers of AKs, but until further evidence is obtained, limiting exposure to UV will continue to be the most effective way of reducing the risk of melanoma.

#### Implications for practice

Of numerous therapies that have been assessed as possible KC skin cancer or melanoma chemopreventives, including topical sunscreen, tretinoin, retinaldehyde, oral retinol, betacarotene, vitamins, isotretinoin, acitretin, nonsteroidal anti-inflammatory drugs, and statins, only regular use of sunscreen has consistent support as a primary preventive agent for SCC and melanoma in the general population [83]. Investigation of the lifetime health costs and benefits of sunscreen promotion in the primary prevention of skin cancers, including melanoma, has shown that routine sunscreen use by white populations who live in sunny climates is likely to be a highly cost-effective investment for governments and consumers over the long term [84].

#### Key points

- There is good evidence that increased sun exposure increases the risk of skin cancer.
- The relationships between sun exposure and BCC and melanoma risk are complex, and observational studies suggest that mechanisms besides cumulative UV exposure are involved.
- Light-skinned people are at much higher risk for skin cancer than those with darker skin.
- There is good evidence that sunscreens can reduce the risk of SCC and melanoma, but sunscreen use alone is not an effective protection strategy against UV.
- There is good evidence to determine that clinician counseling is effective in changing patient behaviors to reduce the risk of skin cancer, particularly in children, adolescents, and young adults 10–24 years.
- Counseling parents may increase their use of sunscreen for children, but there is little evidence to determine the effects of counseling parents on other protective behaviors (clothing, reducing sun exposure, avoiding sun lamps).
- The benefits of sun-protective measures exceed any potential harm.

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# Treatment of cutaneous melanoma

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## Localized disease

### Background

Malignant melanoma (MM) of the skin arises from melanocytes within the epidermis. The tumor can become invasive, penetrate the underlying dermis and subcutaneous fat, and metastasize to distant regions of the body. Rarely, MMs also can arise from other areas of the body, including the retina, meninges, gastrointestinal tract, nasopharyngeal epithelium, and vagina. This chapter is focused on primary cutaneous melanoma.

### Incidence

In 2008, the incidence rate of melanoma worldwide was 1.6% [1]. Specifically, over the past 20 years, the incidence of cutaneous MM of all thickness has increased annually in the Netherlands (4.1%) [2] and the USA (3.1% males, 3.4% in females) [3]. A study in Wales reported a 74% increase in MM over a 3-year period, one of the highest reported increases of MM incidence [4].

While incidence has continued to rise in several countries, reports of mortality from Scotland (1.3 per million per year) [5], Canada (9.8 per 100 000 for males and 8.7 per 100 000 for females) [6], and Australia (8.0 per 100 000 for males and 3.1 per 100 000 for females) [7] suggest that mortality rates may have remained stable or declined in some groups, notably in women. US mortality rates from MM decreased from 2002 to 2006 in men and women younger than 65 years. In contrast, mortality rates have increased for older individuals in the USA (6.6% for men and 0.6% for women) [3, 8]. Reductions in mortality rates may be the result of intensive public education campaigns leading to earlier detection of thinner lesions, with a better prognosis. Early recognition of MM and surgical excision present the best opportunity for cure.

### Risk factors

Several environmental and genetic risk factors confer increased risk for developing melanoma. These risk factors include history of dysplastic nevi [9], increased numbers of common melanocytic nevi [9–11], history of sunburns [10, 12], and family history of melanoma [13, 14]. Genetic risk factors for melanoma include mutations in

*CDKN2A* [15, 16] and *MC1R* [17, 18], which are associated with familial melanoma.

### Diagnosis

Over 95% of patients with MM report a history of change in size, shape, or color. Fewer than 50% of patients describe altered sensation and history of bleeding associated with MM [19, 20]. Various clinical guides have been developed to aid the clinical diagnosis of melanoma. Several diagnostic checklists for melanoma exist, such as the ABCDE rule (A, asymmetry; B, irregular border; C, color variegation; D, diameter  $\geq 6$  mm; and E, evolution) [21, 22] and the seven-point checklist [23]. These diagnostic aids may be useful for identifying potential features of MM; however, their sensitivity and specificity are not well established.

While the main clinical features in MM include irregular pigmentation and shape, significant variations in clinical presentation exist. Dermoscopy can aid diagnosis, but training and experience are required to maximize its usefulness [24]. Newer digital imaging systems have been developed to aid in the diagnosis of pigmented lesions [25].

### Prognosis

The prognosis of localized MM depends on a number of factors, including sex, age, tumor site, and ulceration, but the most significant prognostic factor is the Breslow thickness [26]. This is a measurement of the tumor from the granular layer of the epidermis down to the depth of tumor invasion. In 2010, melanoma staging was modified by the American Joint Committee on Cancer. The changes included the addition of the dermal mitotic rate as a prognostic parameter. Therefore, histologic features that predict survival are (1) Breslow thickness, (2) presence of ulceration, and (3) mitotic rate defined by the number of dermal mitoses per square millimeter [27–29].

With excision, MMs that are less than 1 mm in depth have excellent prognosis with approximately 96% 20-year survival rates [30]. For patients with MM of intermediate thickness (1–4 mm), sentinel lymph node biopsy (SLNB) serves as an important prognostic factor. Positive SLNB predicts a significant reduction in 5-year

survival (72.3% vs 90.2% in SLNB negative) [31]. The involvement of regional lymph nodes with metastases at presentation is associated with survival rates of 25–50% [32]. Tumors deeper than 4 mm are associated with approximately 33–55% survival rates [33]. Prognosis for metastatic MM is discussed in detail in the “Metastatic malignant melanoma” section.

### Treatment objectives

The main aims of surgical treatment are to excise MMs with adequate margins but without creating large postsurgical defects unnecessarily. Various systemic treatments were designed to increase overall survival and progression-free survival, which is defined as the period until recurrence of the primary lesion or distant metastatic spread.

### Methods of search

Medline, PubMed, and Cochrane library databases were searched between the periods January 1966 to June 2012. We retrieved additional relevant literature from the reference lists of the initially identified articles.

### Questions

#### What are the recommendations for surgical excision margins based on the Breslow thickness of the melanoma?

Breslow thickness represents the depth of invasion of cutaneous melanoma from the granular layer. It is the best indicator of prognosis in primary cutaneous MM [26]. Most clinical trials use the Breslow thickness to categorize patient groups. Based on the results of these trials, surgical margins for excision of MM have decreased over the past 20 years.

#### Efficacy

**Melanoma in-situ** No randomized controlled trials (RCTs) have been conducted to determine optimal surgical margins for melanoma in-situ. In 2011, the American Academy of Dermatology published guidelines of care for the management of primary cutaneous melanoma that recommended a 0.5–1 cm margin for surgical excision of melanoma in-situ [27].

**Melanoma with Breslow thickness <2 mm** The World Health Organization Melanoma Group randomized 612 patients with melanomas less than 2 mm in depth to either 1 cm or 3 cm margins from surgical excisions [34]. The 12-year survival rate of patients randomized to the 1 cm margin arm of the study was not statistically significant when compared with those who underwent excision with 3 cm margins (87.2% and 85.1%,  $P = 0.77$ ). Local recurrence rates were also not statistically significant between the 1 and 3 cm margin study arms (2.6% vs 0.1%,  $P$  value not reported) [34].

The Swedish Melanoma Study Group randomized 769 patients with MM with Breslow depth of 0.8–2.0 mm to either 2 or 5 cm resection margins [35]. In comparison with patients randomized to 5 cm margin, those allocated to 2 cm margin experienced no differences in overall survival (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.75–1.24) or relapse-free survival (HR, 1.02; 95% CI, 0.8–1.30). A similar study comparing 2 cm versus 5 cm excision margins for MM less than 2.1 mm thick concluded that the wider margin of 5 cm had no impact on either the overall or disease-free survival compared with 2 cm margins [36]. The disease-free survival rates at 10 years were 85% for the 2 cm group and 83% for the 5 cm group ( $P = 0.83$ ). The corresponding results for overall sur-

vival rates at 10 years were 87% and 86% ( $P = 0.56$ ) [36]. There were no significant differences in local recurrence rates or overall survival between the 2 or 5 cm margins for MM less than 2 mm thick in any of the trials [35, 36].

**Melanoma with Breslow thickness >2 mm** Few studies investigate optimal surgical margins in melanomas thicker than 2 mm [37–39]. A multicenter RCT compared 2 cm versus 4 cm surgical excision margins in patients with cutaneous melanoma thicker than 2 mm [37]. Overall survival at 5 years was 65% in the 2 cm group (95% CI, 60–69%) compared with 65% (95% CI, 40–70%) in the 4 cm excision group [37]. Wider margins of 4 cm did not result in improvement of disease-free survival or overall survival rates. A retrospective observational study of 278 patients with thick MMs (median thickness 6 mm) suggested that 2 cm margins were adequate for thick primary melanomas [39].

A US multi-institutional study randomized 486 patients with intermediate-thickness MMs (1–4 mm in depth) to either 2 or 4 cm margins [40]. The median follow-up period was 6 years. The local recurrence rates were not significantly different between the two groups, with 0.8% in the 2 cm margin group and 1.7% in the 4 cm group. The overall survival rates over 5 years were not significantly different between the two groups at 79.5% for the 2 cm group and 83.7% for the 4 cm group [40].

A British RCT of surgical margins in cutaneous melanoma compared 1 and 3 cm margins for patients with MM 2 mm or greater in depth [41]. A total of 900 patients were enrolled; 453 had excisions with 1 cm margin, and 447 underwent excisions with 3 cm margin, with a median follow-up of 5 years. Patients randomized to the 1 cm margin had an increased risk of locoregional recurrence compared with those randomized to 3 cm surgical margin (HR, 1.26; 95% CI, 1.00–1.59;  $P = 0.05$ ). Overall survival was similar in the two groups; compared with those who received 3 cm surgical margin, the risk for death for those randomized to the 1 cm surgical margin group was not significantly elevated (HR, 1.07; 95% CI, 0.85–1.36;  $P = 0.6$ ) [41].

#### Drawbacks

Wider excisions of MM are not necessarily associated with improved disease-free survival or overall survival. Excisions with wider margins may be associated with significant morbidity and require extensive skin grafting [40]. The Melanoma Intergroup Trial found that the use of skin grafting could be reduced by 75% if 1 cm surgical margin is employed rather than 3 cm margins [40].

A British multicenter trial comparing 1 and 3 cm margins in patients with MM deeper than 2 mm showed that, although overall survival was similar for both groups, those who had the narrower 1 cm margins were more likely to develop locoregional metastases (HR, 1.26; 95% CI, 1.00–1.59;  $P = 0.05$ ) [41]. These results suggest that narrow margins in patients with melanoma thicker than 2 mm may carry an increased risk of locoregional metastasis.

#### Comment

To date, no controlled trials have examined the effect of varying surgical margins on outcomes in MM with Breslow thickness <0.75 mm or those >4 mm. Melanoma in-situ has nearly no potential for metastatic spread [42]. The current consensus is that it is appropriate to excise melanoma in-situ with a margin of 5 mm to 1 cm of clinically normal skin to obtain a clear histological margin [27].

For MM with less than 2 mm Breslow thickness, the preponderance of evidence shows that there are no significant differences in

local recurrence or survival between those treated with narrower surgical margins and those who underwent more extensive surgical excision. Studies have found that MMs <1 mm in depth can be appropriately treated with surgical margins of 1 cm and that MMs between 1 and 4 mm in depth can be appropriately treated with margins of 2 cm [34–37]. In patients presenting with Breslow thickness 2 mm or greater, surgical excision with 1 cm margins may result in increased locoregional metastases [41]. For thicker tumors greater than 4 mm, one observational study found that 2 cm margins may be sufficient [39].

### How should patients with lentigo maligna or lentigo maligna melanoma be managed?

Lentigo maligna (LM) refers to an atypical melanocytic proliferation entirely confined to the epidermis. LM usually occurs on sun-exposed sites, such as the face and neck, of elderly patients [43]. It represents the early evolutionary, in-situ phase of lentigo maligna melanoma (LMM) [44]. The risk of progression from the precursor phase to dermal invasion and the development of LMM is approximately 5% [45]. The period for the development of LM to LMM varies widely from approximately 10 years to greater than 50 years [46, 47].

Management of patients with LM or LMM can be challenging. Patients with these lesions tend to be elderly, with other comorbidities that may limit extensive surgery. The affected areas can be large and occur within close proximity of critical anatomical structures. Histological changes within the epidermis may occur at some distance from the clinically apparent borders [44]. For these reasons, full surgical excision with suitable margins may be difficult or even impossible in some patients.

### Efficacy

LM and LMM are discussed separately below.

#### Lentigo maligna

**Surgery** There have been no RCTs examining optimal resection margins in patients with LM. Surgical treatment modalities used to treat LM include wide local excision, Mohs micrographic surgery, and staged excision. Owing to subclinical extension, determining adequate surgical margins for LM may be difficult, and the post-surgical defect may be 2–10 times larger than the original lesion [48].

Surgical treatment of LM with a thorough margin assessment may reduce clinical recurrence. One study examining the use of Mohs surgery in 26 patients with LM reported no recurrences after a median follow-up of 58 months [49]. A retrospective follow-up study using a staged excision technique showed long-term disease-free survival of 95% [50]. The 59 subjects were followed up for a median of 54 months. The authors reported that three had local recurrences and none had distant metastases [50]. In a study of 42 cases of LM that were followed for a period of 3.5 years, there was a recurrence rate of 9% (2/22) following surgical excision, compared with 35% (7/20) with other techniques, such as radiotherapy (3/8), curettage and electrodesiccation (2/8), and cryotherapy surgery (2/4) [51].

**Cryotherapy** There have been no RCTs examining efficacy of cryotherapy for the treatment of LM. Recurrence rates in patients with LM treated with cryotherapy range from 6.6 to 15% [52, 53]. In a small study, 3/20 patients with LM (15%) experienced recurrence after treatment with cryotherapy with a follow-up period that

varied from 7 to 80 months [53]. The authors reported no clinical evidence of recurrence after patients were retreated with cryotherapy (14-month follow-up period) [53].

**Radiotherapy** There have been no RCTs assessing the efficacy of radiotherapy for LM. A study of 593 patients showed 88% complete clinical clearance after one treatment by Grenz rays at follow-up (ranged from 2 to 5 years) [54]. One case series of 68 patients treated with conventional fractionated radiation therapy with superficial X-ray reported two recurrences after a 5-year follow-up [55].

**Other treatments** There have been a few case reports on the use of various laser treatments in LM, but the sample sizes were too small to yield definitive conclusions. A report of three patients with LM treated topically with 5-fluorouracil showed a 100% recurrence rate after 22, 24, and 42 months of follow-up [56]. A similar report of four cases of LM treated with topical tretinoin showed no benefit [36]. Several case reports and small series reported the use of topical imiquimod 5% cream in patients with LM [57, 58]. In one study, 28 patients showed no relapse after a year, and another study reported successful treatment of six patients, with a follow-up of 3–18 months.

#### Lentigo maligna melanoma

**Surgery** No RCTs have been conducted assessing comparative efficacy of various surgical approaches in patients with LMM. A retrospective study of 117 patients treated with staged excision showed a mean surgical margin of 10.3 mm for excision of LMM [44]. A case series of 26 patients with LM and 19 patients with LMM were treated using Mohs micrographic surgery [49]. The authors reported a 100% cure rate after 29 months and a 97% cure rate after 58 months. The 5-year survival rate for invasive LMM is 85%, which is the same as that for any other type of melanoma with the same thickness [59].

**Radiotherapy** An uncontrolled follow-up study examined fractionated radiotherapy in 64 patients with LM and 22 with LMM following excision [60]. Among the 64 patients with LM, none showed signs of recurrence after a mean follow-up period of 23 months. Among the 22 patients with LMM who underwent fractionated radiotherapy, there were two recurrences [60].

### Drawbacks

Surgery and other destructive methods including cryosurgery, radiation, and laser, may result in morbidities such as scarring, deformity, and pigmentary changes. Surgical excision is the mainstay of therapy for LM and LMM; however, surgical intervention may result in large defects [48]. Cryotherapy may lead to inadequate destruction of melanocytes extending down hair follicles. There have been reports of recurrences, sometimes amelanotic in type, following cryotherapy [61]. The use of imiquimod has been associated with a brisk inflammatory response, which is reflected clinically by erythema, swelling, and crusting of the skin [62]. The existing studies investigating treatment of imiquimod in LM utilize inadequate follow-up periods to assess long-term cure rates.

### Comment

A survey of dermatologists in the UK revealed wide variations in practice patterns for LM and LMM [63]. After reviewing the current treatments for LM, Mahendran and Newton-Bishop devised an algorithm that advocates surgery as the initial treatment of choice. Mohs surgery may be particularly useful for LM and LMM lesions

with indistinct margins and large size. Because prognosis of LMM is the same as other subtypes of melanoma with the same Breslow thickness, the same surgical margins are to be used based on melanoma studies inclusive of all subtypes. For lesions that are not amenable to surgical resection, other therapies such as cryotherapy or radiotherapy may be considered for LM [63].

There is a lack of data on the rate and duration of progression of LM to LMM. Elderly patients with LM and multiple comorbidities need to be closely monitored. However, the appropriate interval for follow-up is currently unknown. Follow-up intervals of 6–12 months may not be sufficient for detection of invasive LMM [64].

### What is the role of sentinel lymph-node biopsy?

SLNB involves the identification and biopsy of the initial site of lymph-node drainage from the primary cutaneous melanoma. Injecting blue dye and/or radiolabeled colloid into the skin surrounding the primary melanoma identifies the sentinel node [65]. This reliable technique allows the identification of patients with micrometastases affecting the regional lymph nodes in up to 97% of cases [66].

### Efficacy

To date, the largest clinical trial assessing the effect of SLNB on overall survival and prognosis is the Multicenter Selective Lymphadenopathy Trial (MSLT) [67]. From 1994 to 2002, 1269 patients with clinically localized intermediate-thickness (1.43 median thickness) primary melanoma were randomized to either (1) wide excision and SLNB or (2) wide excision and observation. Melanoma-specific 5-year mortality was not significantly different between the SLNB group and the observation group (87.1% vs 86.6%) [31]. However, at 5 years, the distant disease-free survival was significantly improved in the SLNB group compared with the observation group (78.1% vs 73.1%;  $P = 0.009$ ).

SLNB is considered a reliable indicator of prognosis and was incorporated in the American staging system for MM (the 2002 American Joint Committee on Cancer staging) [68]. Data from MSLT-I revealed prolonged disease-free survival (83.2% vs 53.4%;  $P < 0.001$ ) and lower 5-year mortality (9.7% vs 26.2%) in those with negative SLNB compared with those with a positive SLNB. In patients with negative SLNB results, the rates of nodal recurrence ranged from 3.4 to 4.1% after median follow-up of 35–58.9 months [31, 69].

Gershenwald *et al.* demonstrated that, in the 580 patients with median MM thickness of 1.80 mm, 15% of patients were found to have lymph node involvement of MM upon SLNB [70]. This study showed that sentinel-node status was the most significant prognostic factor in predicting disease-free survival. While tumor thickness and ulceration predicted survival in sentinel-node-negative patients, they provided no additional prognostic information in sentinel-node-positive patients [70].

The psychological benefits of obtaining accurate staging for patients have not been studied extensively. One questionnaire-based study involving 110 patients showed increased reassurance and satisfaction in those who underwent SLNB, regardless of the result of the biopsy [71].

### Drawbacks

A meta-analysis reviewed complications in 437 sentinel node biopsies in 269 patients with MM from 1994 to 2009 [72]. Following SLNB, the reported complication rate was 4.26%. Observed complications include wound infection (1.83%), seroma (0.61%), and postoperative pain (0.61%) [72]. When SLNB is followed by com-

plete lymph-node dissection, nearly a quarter of patients experience major or minor complications from the procedure [73].

### Comment

To date, no study has shown a survival benefit in patients who underwent SLNB. However, SLNB is generally accepted as a useful staging procedure in patients with primary cutaneous melanoma without clinically evident lymph node involvement. It is appropriate for patients with melanoma thickness between 1 and 4 mm or melanoma thickness  $\leq 1$  mm associated with high-risk features for metastasis (i.e., evidence of ulceration, mitotic rate  $\geq 1/\text{mm}^2$ , or lymphatic or vascular invasion). The utility of SLNB is controversial in tumors with Breslow's thickness  $> 4$  mm. However, conducting SLNB in patients with melanoma thickness  $> 4$  mm may be of prognostic benefit and help guide treatment strategies [74].

### Are there any effective adjuvant treatments for malignant melanoma following resection?

Several studies elucidating the mechanism of action of interferon- $\alpha$  (IFN $\alpha$ ) propose that IFN $\alpha$  may have immunomodulatory or antiproliferative effects on MM [75]. Some studies support the role of indirect immunomodulatory mechanisms rather than direct antitumor mechanisms (i.e., apoptosis, anti-angiogenesis, cytotoxic effects) [76]. One study suggested that a possible reduction in regulatory T cells results in increased antitumor activity [75].

The role of IFN $\alpha$  in the treatment of melanoma is limited to adjuvant therapy following resection of high-risk stage II or III melanoma. The different subtypes of IFN $\alpha$  investigated in the melanoma literature are interferon  $\alpha$ -2a (IFN $\alpha$ 2a), interferon  $\alpha$ -2b (IFN $\alpha$ 2b), and pegylated IFN $\alpha$ 2a and IFN $\alpha$ 2b. The advantage of the pegylated form of IFN $\alpha$  is the extended half-life and reduction of dosing interval.

### Efficacy

The benefit of IFN $\alpha$  as an adjuvant therapy for high-risk melanoma has been demonstrated in several clinical trials [77]; however, the optimal dose and scheduling intervals have yet to be clearly established. High-dose IFN $\alpha$  regimens usually consist of 20 million IU/m<sup>2</sup> intravenously 5 days/week for 4 weeks followed by 1 million IU/m<sup>2</sup> subcutaneously for 11 months. While high-dose regimens have demonstrated the greatest benefit, intermediate- and low-dose therapies have been investigated to assess efficacy and adverse effect profile. The dose for intermediate IFN $\alpha$  varies between 10 million IU five times/week for 4 weeks, then either 10 million IU three times/week for 1 year or 5 million IU three times/week for 2 years [78]. Other intermediate-dose regimens include pegylated IFN $\alpha$ 2b 6  $\mu\text{g/kg}$  per week for 8 weeks, then 3  $\mu\text{g/kg}$  per week for 5 years [79]. Low-dose IFN $\alpha$  typically consists of 3 million IU subcutaneously for 3 days/week for 18 months.

**High-dose interferon** An RCT of 287 patients with MM greater than 4 mm thickness showed significant improvement in disease-free and overall survival in those treated with high-dose IFN $\alpha$ 2b treatment (intravenous 20 million IU/m<sup>2</sup> 5 days/week for 1 month, then subcutaneous 10 million IU/m<sup>2</sup> three times/week for 11 months) compared with surgery alone [77]. After 7 years of follow-up, the median relapse-free time in the high-dose IFN $\alpha$ 2b group was 1.70 years, compared with 0.98 years in those treated with surgery alone ( $P = 0.002$ ). The median survival time in the high-dose IFN $\alpha$ 2b group was 3.8 years, compared with 2.8 years in those treated with surgery alone ( $P = 0.002$ ) [77].



A large three-arm study of 642 patients showed no statistically significant differences in the overall survival of patients treated with either (1) high-dose IFN $\alpha$  for 1 year (20 million IU/m<sup>2</sup> per day for 5 days/week for 4 weeks and then 10 million IU/m<sup>2</sup> subcutaneously 3 days/week for 48 weeks), or (2) low-dose IFN $\alpha$  for 2 years (3 million IU/day 3 days/week), or (3) compared with no therapy [80]. An observational study from the same authors compared high-dose IFN $\alpha$ 2b with vaccine treatment (GM2-KLH/QS-21) in patients with resected stage IIB–III melanoma of the skin [81]. A total of 880 patients were randomized to high-dose IFN $\alpha$ 2b (intravenous 20 million IU/m<sup>2</sup> per day for 5 days/week for 4 weeks and then 10 million IU/m<sup>2</sup> subcutaneously TIW for 48 weeks) and vaccine. Compared with those receiving the vaccine, patients receiving IFN $\alpha$ 2b had significantly improved relapse-free survival (HR, 1.47; 95% CI, 1.14–1.90;  $P = 0.0015$ ) and overall survival (HR, 1.52; 95% CI, 1.07–2.15;  $P = 0.009$ ) [81].

**Intermediate-dose interferon** In an RCT, 1388 patients with thick primary melanomas (>4 mm depth) or regional lymph-node involvement were randomized to receive IFN $\alpha$ 2b for either 13 months or 25 months or observation [78]. The treatment regimen was 4 weeks of 10 million units of subcutaneous IFN $\alpha$ 2b followed by either 10 million IU of IFN $\alpha$ 2b 3 days/week for a year or 5 million IU 3 days/week for 2 years. After a median follow-up of 4.65 years, those randomized to the IFN $\alpha$ 2b treatments did not have significantly improved distant metastasis-free survival or overall survival compared with observation alone. Therefore, in this subset of patients, the authors could not recommend the use of intermediate-dose IFN $\alpha$ 2b [78].

Another study investigating intermediate-dose adjuvant therapy consisted of 855 patients with stage IIB–IIC or III melanoma [82]. Patients were randomized to (1) IFN $\alpha$ 2b 10 million IU dose subcutaneously 5 days/week for 4 weeks followed by IFN $\alpha$ 2b 10 million IU dose subcutaneously 3 days/week for 12 months; or (2) IFN $\alpha$ 2b 10 million IU dose subcutaneously 5 days/week for 4 weeks followed by IFN $\alpha$ 2b 10 million units flat dose subcutaneously 3 days/week for 24 months; or (3) observation only. The authors reported no significant improvement of overall median survival in patients treated with IFN $\alpha$ 2b compared with observation (56.1 months, 72.1 months, and 64.3 months, respectively;  $P = 0.60$ ) [82].

**Low-dose interferon** Several clinical trials have used low-dose subcutaneous IFN $\alpha$  (3 million IU three times weekly) in patients presenting with MMs greater than 1.5 mm thick but with negative lymph nodes [83–85]. In one trial of 499 patients, relapse-free survival and overall survival were compared in patients treated with low-dose IFN $\alpha$ 2a for 18 months and no treatment [83]. There was a significant 25% extension of the relapse-free survival time from 1.3 to 2.1 years ( $P = 0.03$ ). The 5-year relapse rates were 43% for the IFN $\alpha$ 2a group and 51% for the control group. The 5-year death rates were 24% in the IFN $\alpha$ 2a group and 32% in the control group [83].

Another low-dose trial randomized 311 patients to receive IFN $\alpha$ 2a (3 million IU subcutaneously daily for 3 weeks followed by 3 million IU subcutaneously 3 days/week for 12 months) versus observation after surgical removal of the melanoma [84]. At approximately 41 months, 24% of those treated with IFN $\alpha$ 2a developed metastases compared with 36% of the observation arm ( $P = 0.02$ ). The statistically nonsignificant difference in mortality rate was 11% in the IFN $\alpha$ 2a compared with 13% in the observation arm ( $P$  value not reported) [84].

A randomized controlled study examined overall survival and disease-free survival in 674 patients with MM greater than 4 mm in depth or with locoregional metastases [86]. These patients were randomized to either (1) low-dose treatment with IFN $\alpha$ 2a (3 million IU 3 days/week for 2 years or until recurrence) or (2) no adjuvant treatment. There were no differences in the overall survival ( $P = 0.6$ ) or disease-free survival ( $P = 0.3$ ) [86].

### Drawbacks

Adverse effects significantly limit the use of high-dose IFN $\alpha$ . Toxicity and withdrawal from therapy are frequently reported in the high-dose IFN $\alpha$  studies [87]. Treatment-related deaths have been reported [55]. Ten percent of patients treated with high-dose IFN $\alpha$  discontinued treatment because of adverse events [57]. The most frequent adverse effects associated with high-dose IFN $\alpha$ 2b include 10% of people experienced significant toxicity as well as mild symptoms such as nausea and flu-like symptoms [88].

Patients on IFN $\alpha$  therapy may develop autoimmune-like diseases, including the development of autoantibodies, thyroid dysfunction, and vitiligo [89, 90]. However, the development of autoimmunity may correlate with improved prognosis [89].

### Comments

While adjuvant therapy with IFN $\alpha$  may not confer a significant benefit on overall survival, high-dose IFN $\alpha$  appears to improve relapse-free survival significantly. A comprehensive meta-analysis of the data on adjuvant treatment with IFN $\alpha$  has demonstrated a dose-dependent effect on recurrence-free survival and a statistically nonsignificant effect of benefit for overall survival [64].

### Key points: localized disease

- The incidence of cutaneous MM continues to rise worldwide.
- The main treatment for primary cutaneous melanoma is surgical excision.
- The recommended surgical margin for excision of melanoma in-situ is between 5 and 1 mm.
- MM 1–4 mm of depth can be appropriately treated with surgical margins of 1 cm and MM >4 mm in depth with 2 cm margins.
- Data are lacking on effective treatments for LM and LMM.
- SLNB is a useful staging tool, but it does not appear to improve overall survival.
- High-dose IFN $\alpha$ , used as adjuvant treatment, improves disease-free survival, but its benefit in overall survival is marginal. Dose-dependent adverse effects limit the use of IFN $\alpha$ .

### Metastatic malignant melanoma

Metastatic MM (stage IV melanoma) is defined by dissemination of the cutaneous tumor to other organs or nonregional lymph nodes. The most common initial sites of metastasis are the skin, subcutaneous tissues, and lymph nodes in 59% of patients [91]. When MM metastasizes to distant organs hematogenously, it is among the most aggressive malignancies and carries poor prognosis. The skin (38%), lung (36%), liver (20%), and brain (20%) are the most common sites for distant metastasis of cutaneous melanoma [91].

**Table 31.1** Comparison of single-agent dacarbazine with the Dartmouth regimen of combination chemotherapy.

	Dacarbazine	Dartmouth regimen
Response rate (%)	9.9	16.8
Median survival in months (95% CI)	7.7 (5.4–8.7)	6.3 (5.4–8.7)
1-year survival (%)	27	22

The median survival time for patients with metastatic disease (stage IV) is approximately 7 months; the estimated 5-year survival rate is 6% [92]. Predictors of decreased survival include poor performance status, increasing number of organ involvement, liver involvement, and non-liver visceral involvement (Table 31.1) [93]. Elevated serum markers, LDH and S100B, are also negative prognostic factors for patients with distant metastasis [94].

**Questions**

**What therapies improve overall survival in patients with metastatic malignant melanoma?**

The US Food and Drug Administration (FDA) approved high-dose interleukin-2 (IL-2) for the treatment of metastatic melanoma in 1998. IL-2 is an immunomodulatory agent that may function by stimulating T cell populations to elicit an antitumor immune response [95]. Of the patients who respond to IL-2, approximately 7% achieve complete response and remission for up to 8 years [96]. Use of IL-2 therapy is limited by severe toxicity (see Drawbacks section).

In 2011, the FDA approved ipilimumab and vemurafenib for the treatment of metastatic melanoma. Immunotherapies that target cytotoxic T-lymphocyte antigen-4 (ipilimumab) or inhibit the MAP kinase pathway (vemurafenib) have both shown significant improvement of overall survival in patients with disseminated disease [97–99].

**Efficacy**

**High-dose interleukin-2** The recommended dose for high-dose IL-2 is intravenous 600 000–720 000 IU/kg every 8 h for a maximum of 14 doses. One study treated 134 patients with metastatic melanoma with 720 000 IU/kg intravenously every 8 h for a maximum of 15 doses per cycle (total two cycles) [96]. Seven percent of patients with metastatic melanoma achieved complete regression and 14 patients (10%) had partial regression after treatment with high-dose IL-2 after 28 months follow-up.

A phase III study involving 185 patients with advanced stage III or stage IV cutaneous MM compared (1) IL-2 alone (720 000 IU/kg of body weight per dose) versus (2) gp100:209-217(210M) plus incomplete Freund’s adjuvant (Montanide ISA-51) once per cycle, followed by IL-2 [100]. Compared with those randomized to the IL-2-only arm, those receiving combined vaccine and IL-2 arm showed significant improvement in the overall clinical response (16% vs 6%,  $P = 0.03$ ), as well as increased progression-free survival (2.2 months, 95% CI, 1.7–3.9 vs 1.6 months, 95% CI, 1.5–1.8;  $P = 0.008$ ). Additionally, the median overall survival time was increased in the combined vaccine and IL-2 arm compared with in the IL-2-only arm (17.8 months, 95% CI, 11.9–25.8 vs 11.1 months, 95% CI, 8.7–16.3;  $P = 0.06$ ) [100].

**Ipilimumab** Ipilimumab is a human monoclonal antibody that binds cytotoxic T-lymphocyte antigen-4 to decrease tumor tolerance via upregulation of antitumor T-cell responses. In phase III trials, improvement in overall survival was seen in patients treated with ipilimumab when used as monotherapy (compared with glycoprotein 100 (gp100) vaccine) or when used in conjunction with dacarbazine (dimethyltriazenoimidazole carboxamide) compared with placebo combined with dacarbazine [97, 98]. In one study, 676 patients with previously treated unresectable metastatic melanoma were randomized to (1) ipilimumab (3 mg/kg of body weight) with gp100 vaccine, (2) ipilimumab alone, or (3) gp100 alone once every 3 weeks for four treatments [97]. The authors reported a significant increase of approximately 4 months in overall survival among patients receiving ipilimumab plus gp100 compared with patients receiving gp100 alone (10.0 vs 6.4 months;  $P < 0.001$ ) [97].

Another study in previously untreated patients with metastatic melanoma showed significantly increased overall survival in patients receiving ipilimumab (10 mg/kg every 3 weeks for four doses) and dacarbazine (850 mg/m<sup>2</sup> every 3 weeks for up to 22 weeks) compared with those who received placebo and dacarbazine (47% vs 36% at 1 year follow up;  $P < 0.001$ ) [98].

**Vemurafenib** Vemurafenib, a selective inhibitor of *BRAF* mutations, showed similar efficacy in patients with metastatic melanoma. A phase III study that enrolled 675 patients with MM containing V600E mutation in *BRAF* compared vemurafenib with dacarbazine in patients with unresectable stage IIIC or metastatic disease. The interim analysis revealed lower mortality (HR, 0.37; 95% CI, 0.26–0.55) and lower tumor progression (HR, 0.26; 95% CI, 0.20–0.33) in those treated with vemurafenib compared with dacarbazine [99].

**Drawbacks**

The choice of appropriate immunotherapy varies depending on MM characteristics and patients’ baseline comorbidities. Potential adverse events due to IL-2 include nausea, diarrhea, hypotension, and hepatic and renal dysfunction [96].

Risks associated with ipilimumab therapy include severe immune-mediated reactions (i.e., hepatitis, enterocolitis, endocrinopathies), and therefore ipilimumab should be avoided in patients with autoimmune diseases or organ dysfunction [97, 101]. Transient exacerbation of disease, manifesting as new MMs or progression of pre-existing MMs, may be observed in approximately 10% of patients on ipilimumab prior to achieving therapeutic response [102].

Vemurafenib is indicated only in patients with melanomas with a V600E mutation in *BRAF*. Eruptive keratoacanthomas and squamous cell carcinoma are reported during initial weeks of therapy with *BRAF* inhibition due to paradoxical activation of MAP kinase pathway [99, 103].

**Comments**

The advent of novel immunotherapies has ushered a greater number of treatment options for patients with metastatic MM. Therapy with IL-2 may result in complete remission for <11% of metastatic melanoma patients [104]; however, the toxicity of this treatment limits its use to healthier individuals without end organ damage. Treatments with ipilimumab and vemurafenib have shown improved progression-free survival and overall survival. Owing to the potential for severe immune-mediated adverse effects, ipilimumab is most appropriate for patients without history of autoimmune

disease and organ dysfunction. The use of vemurafenib is limited to melanomas that harbor the V600E mutation in *BRAF*.

### Which chemotherapeutic agents are effective in treating metastatic melanoma? Are combination therapies effective?

#### *Efficacy*

Dacarbazine is an FDA-approved chemotherapeutic agent for the treatment of metastatic melanoma. Dacarbazine is an alkylating agent which functions by inducing DNA strand breakage and apoptosis. Historically, dacarbazine is considered to be the standard treatment against which newer therapies are evaluated [105]. When used as monotherapy for metastatic melanoma, dacarbazine results in partial response (>50% regression for at least 4 weeks) rates of about 20%, complete responses (total regression of measurable disease for at least 4 weeks) in 3–5%, and long-term remissions in fewer than 2% of patients [106]. It is usually given intravenously at 850–1000 mg/m<sup>2</sup> on day 1 every 3 weeks [98, 107, 108] or 200 mg/m<sup>2</sup> on days 1–5 every 4 weeks [109, 110].

Temozolomide is an oral alkylating agent with a broad spectrum of antitumor activity. It has 100% oral bioavailability and good penetration of the blood–brain barrier and cerebrospinal fluid. Temozolomide has been studied off-label for the treatment of MM. The most commonly administered dose in clinical trials is 150–200 mg/m<sup>2</sup> for 5 days every 4 weeks [111, 112]. Its efficacy is at least equal to that of dacarbazine in metastatic MM [111]. Specifically, the median overall survival for temozolomide is 7.7 months compared with 6.4 months with dacarbazine (HR, 1.18; 95% CI, 0.92–1.52) [111].

#### *Drawbacks*

The dose-limiting toxicities with chemotherapeutic regimens such as dacarbazine and temozolomide are bone-marrow suppression and nausea/vomiting, requiring hospital admission or threatening life in 20% and 5% of patients, respectively [113, 114]. To reduce nausea and vomiting, anti-emetic therapy may be administered prior to treatment.

#### *Comments*

Prior to the approval of immunotherapeutic agents ipilimumab and vemurafenib, dacarbazine was the mainstay of therapy for metastatic melanoma. Dacarbazine has been used as a single agent or in combination therapies with other chemotherapy regimens or immunotherapies (see Combination therapy). In clinical studies, dacarbazine monotherapy showed response rates of 5–25% [115]. The combination of dacarbazine with other chemotherapeutic and chemohormonal agents offers no additional survival benefit than dacarbazine alone [113, 116–118].

Another alkylating agent, temozolomide, has shown equal efficacy to dacarbazine [111]. Temozolomide may penetrate the blood–brain barrier and may have some efficacy in central nervous system metastasis [119].

### Does combination chemotherapy help?

#### *Efficacy*

Many other drugs – such as platinum agents, vinca alkaloids, nitrosoureas, and taxanes – have been tried alone and in various combination regimens. It remains unclear whether certain combination therapies offer significant survival advantage over single-agent therapy with dacarbazine. In one study, a response rate of 55% was reported for the combination of dacarbazine, cisplatin, carmustine,

and tamoxifen (Dartmouth regimen) [120]. However, in a multicenter RCT comparing the Dartmouth regimen with single-agent dacarbazine, the investigators found no significant survival advantage and only a small, nonsignificant increase in tumor response (Table 31.1) [113].

Hormonal therapy using tamoxifen, an estrogen receptor-blocking agent widely used to treat breast cancer, has been used in combination with cytotoxic agents to modify the tumor response. One study in 117 patients showed greater efficacy of combining tamoxifen with dacarbazine compared with dacarbazine alone (response rates 28% vs 12%, respectively,  $P = 0.03$ ; median survival 48 weeks vs 29 weeks,  $P = 0.02$ ) [121]. Unfortunately, these results were not replicated in a four-arm RCT involving 258 patients with metastatic MM comparing (1) dacarbazine alone, (2) dacarbazine plus IFN $\alpha$ , (3) dacarbazine plus tamoxifen, or (4) dacarbazine plus IFN $\alpha$  and tamoxifen. Response rates were 19% (95% CI, 12–26) for patients receiving tamoxifen and 18% in the non-tamoxifen group (95% CI, 12–25) [114].

Whether the antitumor responses from existing systemic therapy can be boosted by the addition of immunotherapy is an area of active investigation [122, 123]. One meta-analysis compared (1) dacarbazine-containing treatments, (2) non-dacarbazine-containing regimens, and (3) chemotherapy combined with immunotherapy in metastatic MM [123]. The meta-analysis included 12 RCTs with a total of 3273 patients. The addition of IFN $\alpha$  to dacarbazine increased the response rate by 53% over dacarbazine alone (95% CI, 1.10–2.13). Dacarbazine-containing combination therapy was associated with a better response rate when compared with dacarbazine monotherapy (odds ratio, 1.23; 95% CI, 1.02–1.48). Despite the modest increase in response rates, there was no overall survival advantage for combination treatment compared with dacarbazine monotherapy.

#### *Drawbacks*

Bone-marrow suppression, nausea, vomiting, and fatigue were significantly more common with the Dartmouth combined therapy than dacarbazine alone [113]. Common adverse events during tamoxifen therapy include hot flushes, vaginal dryness, and sleep disturbances. Serious adverse events such as thromboembolic events, pulmonary embolism, and endometrial cancer may occur as a result of tamoxifen therapy [124].

Interferons commonly cause malaise, fevers, and flu-like symptoms. High-dose IFN $\alpha$  caused significant (greater than grade 3) myelosuppression, hepatotoxicity, and neurotoxicity in 24%, 15%, and 28% of the patients, respectively [77]. With low-dose IFN $\alpha$ , 10% of people experienced serious adverse events [88].

#### *Comment*

The evidence to date is insufficient to support the use of combination chemotherapy using dacarbazine with the addition of cytotoxic chemotherapy (i.e., vinblastine, cisplatin, paclitaxel) or hormonal therapy (i.e., tamoxifen) as first-line therapy for metastatic melanoma.

### Does antisense therapy against B-cell lymphoma 2 improve outcomes in patients with metastatic melanoma?

#### *Efficacy*

Oblimersen is an antisense molecule that targets B-cell lymphoma 2 (Bcl-2); it is a key inhibitor of the mitochondrial apoptosis signaling pathway. In a randomized trial, 771 patients were randomized to receive single-agent dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks with



or without oblimersen 7 mg/kg per day for 5 days every cycle [125]. The response rates were higher in patients receiving combination of dacarbazine with oblimersen (12.4% vs 6.8%;  $P = 0.007$ ), and there was a trend towards improved median survival (9 vs 7.8 months;  $P = 0.077$ ).

### Drawbacks

Bcl-2-targeted therapy is associated with neutropenia, thrombocytopenia, fevers, and an increased risk of thrombosis.

### Comment

Antisense treatment targeting Bcl-2 represents a novel treatment modality and shows promise in early clinical trials. More studies are necessary to fully determine its efficacy and safety profile.

### Clinical implications

Developments in the systemic treatment of melanoma have resulted in improved survival for advance metastatic melanoma (Stage IV). Following the approval of ipilimumab and vemurafenib, dacarbazine is no longer the gold standard of therapy for metastatic melanoma. Studies demonstrate both ipilimumab and vemurafenib significantly increase overall survival in patients with metastatic melanoma [97, 98]. Immunotherapy with IL-2 is associated with the potential of complete remission; however, its use is limited by severe toxicity. The role of cytotoxic chemotherapeutic agents, as monotherapy and in combination regimens, is limited in initial treatment for metastatic melanoma.

#### Key points: metastatic melanoma

- The 5-year survival for patients with metastatic melanoma is 5%.
- Treatment with IL-2 may result in complete remission in 7% of patients after 28 months of follow-up. IL-2 treatment may be associated with severe toxicity, such as hypotension, pulmonary edema, arrhythmia, and rarely death. Its use in patients with organ impairments must be carefully monitored.
- Targeted immunotherapy with ipilimumab and vemurafenib results in significantly prolonged survival benefits and progression-free periods in patients with metastatic melanoma.
- Ipilimumab therapy may result in severe immune-mediated adverse effects, such as endocrinopathy and colitis.
- Vemurafenib is strongly recommended for patients with metastatic melanoma with V600 mutation in *BRAF*.
- Treatment with vemurafenib may result in eruptive keratoacanthomas and squamous cell carcinomas.

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# Treatment of squamous cell carcinoma

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## Background

### Definition

Squamous cell carcinoma (SCC) of the skin, the second most common type of nonmelanoma skin cancer (NMSC), is a malignant tumor arising from keratinocytes in the epidermis (Figure 32.1). Invasive SCC is defined as the passage of atypical keratinocytes through the basement membrane into the dermis and is thus distinguished from potential SCC precursor conditions on an architectural rather than histological basis.

Invasive SCC has the propensity to cause local tissue destruction and may also metastasize to regional lymph nodes or distant organs, occasionally causing death.

The focus of this chapter is nonmetastatic invasive cutaneous SCC. Prevention of SCC is discussed in Chapter 30. Excluded from this chapter are precursor lesions, SCCs of mucosal surfaces (head and neck, lung, gastrointestinal tract, urogenital tract), and SCC of the penis, vulva, and anus.

### Incidence

NMSCs are the most common malignancies in Caucasians, with an approximate ratio in the general population of one SCC to every four basal cell carcinomas (BCCs). Lack of standardization of data collection and incomplete registration of NMSCs confound accurate comparisons of incidence in different regions. However, overall, the incidence of SCC has been increasing around the world since the 1960s [1], although some studies suggest that incidence rates of SCC in some areas may now be stabilizing in subgroups of the population [2–6].

Worldwide, the greatest SCC burden is seen in Australia, where population-based epidemiological surveys suggest age-standardized incidence rates of more than 1000 cases per 100 000 per population per year [7–9]. In the USA, incidence rates are in the range 32–155 per 100 000 population for males and 8–29 per 100 000 population for females [10,11]; although far less than those seen in Australia, these are generally higher than age-standardized rates seen across northern Europe, where recorded incidence rates range from 11–46 per 100 000 per population for males and from 5–23 per 100 000

for females [4,5,12–14]. Variations in incidence are also seen within countries and almost certainly reflect differences in ultraviolet (UV) radiation exposure at different altitudes or the distribution of susceptible ethnic groups within the country [1].

Organ transplant recipients have a 65–253 times greater risk of developing SCC than the general population, with reversal of the usual BCC:SCC ratio [15–18]. In Europe, 10- and 20-year post-transplant cumulative incidences of SCC of 7% and 20% respectively have been reported [19], although corresponding incidences in the Australian organ transplant population are considerably greater, at 52% and 82% respectively [18].

### Etiology

Cutaneous SCC may develop *de novo* in apparently healthy skin, within chronic wounds, scars, burns, ulcers, and sinus tracts, or from the pre-existing lesions listed:

- actinic keratosis (solar keratosis)
- Bowen's disease (intraepidermal SCC)
- arsenical keratosis
- erythroplasia of Queyrat
- Bowenoid papulosis of the genitalia
- actinic cheilitis (leucokeratosis of the lips)
- post-irradiation keratosis
- tar keratosis.

The risk of developing SCC depends on the interrelationship between extrinsic factors and the individual's response to these. Those of advanced age, with red or blond hair, and having a propensity to sunburn rather than tan are at increased risk of developing SCC [20], as are albinos and those with genetic conditions such as xeroderma pigmentosum, in which the capacity to repair UV-induced DNA damage is impaired [10]. Cumulative lifetime exposure to UV radiation, particularly UVB (280–315 nm) from sunlight, is a major factor in the development of SCC [21]. The protective effect of skin pigmentation is reflected in the relatively low incidence of NMSC seen in people with skin types V and VI [22–24]. However, the mortality in this group has been shown to be disproportionately high in comparison with incidence [25]. Whereas the sun-exposed skin of the head and neck is the most





**Figure 32.1** A biopsy-proven neurotropic SCC of the temple.

common site for the occurrence of SCC in fair-skinned populations, non-sun-exposed sites are more frequently involved in those with pigmented skin, suggesting that sunlight exposure is a less important etiological factor in this group. The presence of chronic scarring processes and areas of chronic inflammation are the most important risk factors in skin types V and VI [26,27], and SCCs associated with these predisposing factors tend to be more aggressive, with a 20–40% risk of metastasis compared with a rate of 1–2% in sun-induced SCC [27,28].

In addition to direct DNA damage resulting from the creation of pyrimidine dimers by UV light, mutations in the *ras* oncogene and the p53 tumor-suppressor gene have also been strongly implicated in the development of SCC [29–32]. The role of UVA (315–400 nm) in carcinogenesis is less well understood but of importance, with a positive association between sunbed use and SCC risk having been shown in a systematic review [33]. Although UVA appears to be less mutagenic than UVB and is less efficient at producing cyclobutane pyrimidine dimers and pyrimidine–pyrimidine photoproducts, most UVA damage appears to be indirect through formation of reactive oxygen species and the transfer of energy to DNA via mutagenic oxidative intermediates [34].

There is also good evidence that smoking, exposure to arsenic, ionizing radiation, psoralen–UVA (PUVA) therapy, and petroleum by-products can also promote the development of SCC [35–40]. Serological studies are providing evidence of an association between infection with human papillomaviruses and the risk of developing SCC, although the mechanisms of their etiological role remain unclear and further research is required in this area [41–43].

## Prognosis

For the majority of patients with primary SCC the prognosis is excellent. However, cutaneous SCCs have a much greater propensity than most BCCs to metastasize, and when regional or distant metastases do occur, the prognosis is very poor, with a 10-year survival rate of just 20% for those with regional metastasis and less than 10% for distant metastasis [44].

Rowe *et al.* [28] analyzed data from more than 200 studies published from the 1930s to the 1990s, including all reports in which there was treatment of more than 20 patients with SCC, specified separately from BCC, and in which the results were separated by treatment modality. These studies did not have consistent follow-up intervals, and it is doubtful whether the choice of tumor for each modality was similar; however, some features of SCC became clear. The recurrence rate increased as the length of follow-up increased. The overall local recurrence rate after excision of an SCC involving sun-exposed areas was 8%, while the recurrence rates on the ear and lip were 19% and 11%, respectively. The metastatic rate for primary SCC of sun-exposed areas was 5%, while the rates for SCC on the external ear, lip, and areas not exposed to the sun were 9%, 14%, and 38%, respectively. Previously treated recurrent tumors were also associated with a particularly poor prognosis, with an overall metastatic rate of 30%.

The following prognostic features have been correlated with a poorer prognosis for SCCs, and form the basis of the current American Joint Committee on Cancer tumor staging system which can be used in combination with nodal and metastatic status to stratify patients and guide treatment decisions [45]:

- Tumor diameter >2 cm
- Tumor depth >2 mm thick
- Clark's level ≥IV
- Anatomic site ear/lip
- Perineural invasion
- Histological differentiation poor or undifferentiated.

## Diagnostic tests

Diagnosis of cutaneous SCC is by biopsy or excisional biopsy. Invasive SCC is distinguished from SCC in situ by invasion of the dermis by epithelioid cells in atypical nests and cords, and rarely as single cells. Local draining lymph nodes should always be examined for evidence of regional metastasis.

## Aims of treatment and relevant outcomes

The aim of treatment is to remove or destroy the tumor completely and to minimize cosmetic and functional impairment. Success should therefore be measured by rates of recurrence or metastasis at fixed time points, or by survival analyses that document the time to first recurrences in groups of patients. The morbidity of the procedure, as measured by short-term or chronic pain, infection, scarring, skin function, and overall cosmesis, should all be considered when choosing the appropriate treatment modality. In addition, the cost and tolerance of the specific treatment modalities should be considered.

In general, SCC has not been thoroughly or rigorously studied, and there are very few prospective randomized controlled trials (RCTs) [46].

## Methods of search

The following databases were searched up to the end of May 2012:

- The Cochrane Skin Group Specialised Trials Register
- The Cochrane Central Register of Controlled Trials
- The Cochrane Database of Systematic Reviews
- Medline from 1946
- Embase from 1974
- AMED from inception
- PSYCINFO from inception
- LILACS from inception.



Search terms included squamous cell carcinoma, SCC, skin neoplasms, non-melanoma skin cancer, and NMSC. Reference lists and review articles were scrutinized for articles not identified from the database searches.

Owing to lack of relevant RCTs, data from uncontrolled studies have been included in this chapter with comment as appropriate on the limitations of evidence from such sources.

## Questions

The following questions relate to the treatment of a large (>2 cm) invasive SCC with perineural invasion on the temple of a 60-year-old man:

- What are the effective therapeutic interventions for localized invasive SCC of the skin?
- How do the therapeutic interventions for localized SCC of the skin compare with each other?
- How do cosmetic outcomes for these therapeutic interventions compare?

## Evidence summary

### Surgical excision

Surgical excision is still the primary treatment for invasive SCC, usually performed in the outpatient setting under local anesthesia. The standard excision technique involves estimation of the clinically obvious tumor, either visually or via curetting, although there is little evidence that curettage pre-excision of SCCs is of benefit [47]. The surgeon marks an area of normal-appearing skin as an additional margin to be taken around the tumor, the size of which is determined by the prognostic features of the tumor and in accordance with management guidelines [48,49]. After excision the wound is sutured or allowed to heal by secondary intent using appropriate wound-care regimens. The histology of the tumor is examined in formalin-fixed sections, including a sampling of the margins to assess whether the tumor has been completely removed. Examination of the margins is sometimes carried out in frozen sections, which may be immediately available.

### Efficacy

There have been no RCTs which have compared the effectiveness of surgical excision with other treatment modalities. Evidence of effectiveness comes largely from case series with variable follow-up durations, and variable reporting of tumor size and location, so data have to be interpreted with caution. Recurrence rates from such studies range from 0 to 15% [50–67], with SCC of the ear region showing the greatest propensity to recur both locally and regionally. A greater tendency to recurrence has also been noted with large tumors, with Pless reporting local recurrence in 12% (four of 49) of patients with SCC of the pinna less than 1 cm in diameter up to 43% (three of seven) for those whose SCC was greater than 4 cm [59], although six of the 10 patients who developed metastasis in the series by Mourouzis had SCCs smaller than 2 cm in diameter, suggesting that even the smallest SCCs have metastatic potential. Poor differentiation, location on the pinna, and incomplete excision were found to be independent risk factors for regional metastasis in this study [57]. Deaths attributable to SCC are rare after excision of a tumor which is not known to be metastatic at the time of initial treatment, ranging from 0% in two studies of eyelid SCCs [52,61] up to 8% [51,54,55,62–64] for SCCs at various other cutaneous sites.

Recommendations on the width of the margin of normal-looking skin excised around clinically well-defined tumors ranges from 4 mm to 1 cm [48,49], although there have been no RCTs comparing different excision margins for SCC. One study has assessed the margin size required to clear the subclinical extensions in 95% of 141 SCCs using Mohs micrographic surgery (MMS) in incremental stages, and the UK recommendations of 4 mm for “low” risk and 6 mm for “higher” risk SCC are based on this work [68].

### Drawbacks

Large tumors, or tumors in cosmetically complex areas such as near the eyelids or ears, often require a flap or graft for repair. The subsequent scar from surgical excision usually results in a hypopigmented line, and hypertrophic and keloidal changes may occur. Since the surgical site is most often closed at the time of surgery and histology is later evaluated on fixed tissues, the discovery of residual tumor may mean that the patient has to return for further surgical interventions.

### Comment

Surgical excision is still the major definitive treatment option for SCCs.

### Mohs micrographic surgery

MMS, a technique originally devised by Frederic Mohs in 1941 [69], allows precise definition of the extent of the tumor to ensure maximum removal whilst at the same time conserving normal tissue as much as possible. The procedure is carried out in stages over several hours. The surgeon excises the tumor and a small clinically normal-looking margin, processes the specimen as a frozen section, reads the slides to mark margins with residual tumor, re-excises tissue at the positive margin, and processes the new specimen. These steps are followed until all margins are clear of tumor. This differs from excision with frozen section margin control in four ways. First, the initial specimen is excised as one intact disk with beveled edges, yielding a saucer-shaped specimen. This shape facilitates orientation and preparation for microscopic evaluation. Second, the processing of the specimen is different from the processing of specimens as performed by the pathology department. Horizontal sections are prepared in such a way that the entire margin from the epidermis to the deepest portion of the specimen is viewed under the microscope in very few sections. Third, the surgeon is trained to be a histopathologist as well and reads the slides, allowing him or her to orient any residual tumor relative to other structures in the skin, such as the plane of sebaceous glands or a prominent blood vessel.

Final closure is performed once the entire margin is clear. MMS is considered to be a highly curative procedure for NMSCs, since immediate histopathological evaluation of the entire margin is possible. In addition, histopathologically uninvolved skin is spared, as the mapping technique allows specific reexcision of only the involved margins, limiting potential damage to adjacent tissues.

### Efficacy

There have been no RCTs comparing MMS with other treatment modalities for SCC. Using the fixed tissue technique, Mohs reported an overall 5-year cure rate of 97% for the 1894 patients with previously untreated SCCs, and 76% for the 355 patients with SCCs recurrent after prior treatment [70]. Rowe *et al.* [28] analyzed case series up to the 1990s and found a similar 97% 5-year cure rate for primary SCCs treated by MMS, compared with 92% following

standard surgical excision. For previously treated recurrent SCCs, a 90% 5-year cure rate after MMS also compared well with the 77% rate obtained after surgical excision [28]. Evidence from later case series also suggests that recurrences after MMS are fewer than after conventional surgical excision, with local recurrence of between 0 and 5.7% [65,71–79] during follow-up periods that varied between studies ranging from a mean of 18.5 months to 77 months.

### Drawbacks

MMS is expensive and is not accessible to all patients. Full extirpation of the tumor may require multiple stages over a period of many hours. Patients who cannot lie down due to a comorbid condition may not tolerate the potentially lengthy procedure. In addition, the processing of the frozen sections is labor intensive.

### Comment

MMS appears to have lower recurrence rates than conventional surgical excision and radiotherapy. For low-risk small-diameter SCCs (minimally invasive or in low-risk sites), other treatment modalities should be considered, as there is probably little to be gained in efficacy and much to be lost in terms of cost and time.

### Radiotherapy

A wide variety of radioactive modalities and dosages have been used, with irradiation techniques being adapted to tumor characteristics such as location and size. Radiotherapy for SCC generally involves superficial external irradiation of the lesion and its margins. Uninvolved tissue is protected from radiation by the use of specially fitted lead masks or shields as necessary. Several fractionated doses of radiation are delivered over the course of a few weeks; administration of radiation in a single or a few high-dose fractions is now less commonly used, due to the increased risk of radionecrosis.

Brachytherapy, in which the radioactive source is applied directly to the tumor via a surface mold or interstitial wires, is also sometimes used to treat superficial NMSCs, requiring less protracted treatment times than conventional radiotherapy.

Additionally, radiotherapy may be administered to the tumor bed and occasionally to first-echelon lymph nodes as an adjuvant therapy postoperatively with the aim of eradicating residual tumor cells. The most common indications for using radiotherapy like this are histologically incomplete excision and perineural invasion.

### Efficacy

No standard protocols have been tested and generally adopted for radiotherapy for SCC, and no RCTs have examined the effectiveness of radiotherapy in comparison with other treatments for SCC. Several retrospective studies have examined the role of radiotherapy for SCC. Rowe *et al.* [28] analyzed the literature on SCC of the skin from 1940 to 1992 and found an average local recurrence rate of 10.0% after  $\geq 5$  years in 160 patients who had received radiotherapy for primary SCC. Since 1992, further case series have reported local recurrence of between 6 and 13.6% [80–82] for primary SCCs following external radiotherapy, but long-term follow-up data tend to be limited. In the largest series by Barysch *et al.* [82], in which 177 primary SCCs were followed for a mean of 4.9 years, there were 24 recurrences (13.6%), all of which apart from one were located in the head and neck region. The highest 5-year relapse-free survivals in SCCs were located around the eyes (100%) and cheeks (91%). Several case studies in the radiation oncology literature have noted that increasing tumor size is associated with a progressively decreasing success rate in treating SCC with

radiotherapy. Previous treatment is also a poor prognostic factor [83–87].

Several small open-label series have addressed the use of brachytherapy to treat invasive SCCs [88–93]. The largest study with the longest mean follow-up of 45 months reported local recurrence in two patients of 48 (4.2%) [89], and a further study found one local recurrence of 18 SCCs which were followed for more than 12 months [90]. Although the remaining studies reported no recurrences, only a few patients with invasive SCC were included (total 22 patients) and follow-up was generally limited.

A systematic review of the role of surgery plus adjuvant radiotherapy (ART) in high-risk SCCs found that the 91 patients who received ART were at significantly greater risk of developing regional and distant metastases than the 2358 patients who did not [94]. As the studies included did not incorporate data on tumor staging, it is likely that those who received ART had more advanced disease. Clear surgical margins were only recorded in 8% of ART patients, so there was uncertainty about margin status in the majority.

### Drawbacks

Radiotherapy usually requires multiple treatment sessions, which may make it less convenient for patients. Unlike other standard treatments for SCC, ionizing radiation causes a small increased risk of cutaneous carcinoma within the treatment field [95]. Atrophy, hypopigmentation, alopecia, and telangiectases are also commonly seen late cutaneous sequelae of radiotherapy, yielding an eventual suboptimal cosmetic outcome in spite of excellent early cosmesis [96]. These side effects make this modality of treatment for SCC less desirable for younger patients. Given the risk of radionecrosis, caution should also be exercised when considering radiotherapy for lesions overlying bone or cartilage [97].

The main advantages of radiotherapy include preservation of perilesional normal tissue, and the tolerability of the treatment. Radiotherapy does not require anesthesia, and patients who are medically unable to tolerate or who refuse a surgical procedure may be able to undergo radiotherapy. Radiotherapy appears to be an effective treatment for SCC, particularly for small lesions that have not been previously treated. As tumor-free margins are not assessed during treatment, the treatment sites should be closely monitored at follow-up visits for possible recurrences.

Current evidence is insufficient to identify those high-risk features in which ART may be beneficial.

### Electrodesiccation and curettage

Electrodesiccation and curettage (ED&C) is frequently used in the treatment of SCC, particularly for in situ or minimally invasive lesions on the trunk or limbs. Following tumor debulking by curettage, an electric current is applied through a fine-tipped needle in repeated cycles, causing desiccation of the base and destruction of residual tumor.

### Efficacy

There are no RCTs that have compared the efficacy of ED&C with other treatment modalities. Several case series have reported generally excellent cure rates with reported recurrences of between 0 and 4.2% for SCCs treated at various sites [56,66,98–102]. Follow-up periods ranged from less than 1 year up to a mean of 6.8 years. These series include mostly SCCs perceived as being at low risk of recurrence, which may explain the low recurrence. In the series by Knox *et al.*, which had the greatest number of patients treated by

ED&C, there was one case of recurrence of 545 SCCs with 1 year follow-up, with 90% of treated tumors having a diameter of less than 2 cm [56]. Honeycutt and Jansen treated 281 invasive SCCs with ED&C and noted three recurrences (1.1%) during follow up of 4–8 years. Overall, 264 (94%) of the treated SCCs were smaller than 2 cm in diameter, with one recurrence in this group (0.6%) compared with two recurrences in the 17 patients who had SCCs greater than 2 cm in diameter (11.8%) [99].

One small series by Shiffman in which 15 patients with SCC of the pinna (11 with cartilage invasion at the time of diagnosis) were treated with ED&C, reported local recurrence in three (20%) [62]. Two patients died as a result of their disease, one having developed regional and distant metastases, and the other distant metastases. The success of this technique is thus likely to be partly a reflection of the selection of smaller, less-invasive lesions at anatomical sites which are not considered particularly high-risk areas.

### Drawbacks

Cosmetically, the scar from ED&C is usually a hypopigmented sclerotic circle, rather than the thin line resulting from excision. Although the circular scar often contracts, hypertrophic changes can also occur, making it difficult to recognize recurrent SCC. For SCC lesions on the face, particularly adjacent to critical tissues, contraction of resultant scars may distort or destroy the normal or functional anatomy. In addition, a surgeon performing ED&C at sites adjacent to vital or anatomically complex structures (such as the nose or eye) might limit the margins of destruction or be less aggressive in order to preserve native tissue; this is likely to diminish the effectiveness of this technique. Whelan and Deckers [103] found that the majority (65%) of lesions took 4 weeks to heal after ED&C, while in a separate study they found that the average time for healing was 5.1 weeks [104]. Prolonged healing in comparison with surgical excision should be taken into consideration, particularly for lesions on the lower extremities.

With the ED&C technique, no tissue is obtained that can be examined microscopically to determine whether the margins of the treatment are clear of tumor, and there is no information on prognostic factors such as depth of invasion.

### Comment

ED&C appears to be effective for early low-risk SCC lesions and is rapidly and easily performed by the experienced surgical clinician. Adequate follow-up is essential to recognize the rare recurrences.

### Cryotherapy

Cryotherapy involves the delivery of liquid nitrogen to freeze and thaw tissue, resulting in cellular destruction and local inflammation. A rapid freeze and slow thaw maximizes epithelial cell damage and is most suitable for treating skin tumors. Two or three freeze–thaw cycles are generally employed to treat small, low-risk NMSCs, although much variation in practice exists.

### Efficacy

There are no RCTs that have compared the effectiveness of cryotherapy with other treatments. Several case series have reported no recurrences during follow-up ranging from 1 month to 14 years after treatment of selected low-risk SCCs with cryotherapy [105–110]. In a series of 34 low-risk SCCs, Holt reported one SCC that did not respond to cryotherapy, and one recurrence 13 months after treatment of a tumor on the shin [111]. A cure rate of 97.3% was reported by Graham and Clark for 563 new SCCs, with most of the

included SCCs measuring less than 2 cm [112]. Similarly, of 52 new SCCs treated between 1980 and 1984, Kuflik and Gage reported two (3.8%) recurrences of a nose and an ear SCC, an overall 5-year cure rate of 96.1% [113], with a later series by the same authors reporting no recurrences of 134 SCCs treated by cryotherapy between 1990 and 1996 [108]. SCCs which were treated by cryotherapy in these series were generally highly selected for this particular modality, so it is difficult to compare its efficacy with other treatment modalities.

### Drawbacks

Cryotherapy at an effective dosage is always complicated by an initial period of significant edema, followed by formation of a large bulla. After rupture, the wound weeps and then crusts, taking 4–10 weeks to heal. Delayed and temporary adverse events reported after cryotherapy include hemorrhage, infection, milia, hyperpigmentation, and altered sensation. The development of permanent hypopigmentation and occasional hypertrophic scarring may result in an inferior cosmetic outcome compared with other treatments.

With the cryotherapy procedure, no tissue is obtained for histological examination. Since cryotherapy rarely destroys deep tissues, clinically suspected or biopsy-proven invasion into subcutaneous fat or deeper planes should be considered a relative contraindication.

### Comment

Cryotherapy is effective for treating in situ disease and low-risk SCC but is not appropriate for previously treated recurrent tumors or those with high-risk features.

### Photodynamic therapy

Photodynamic therapy (PDT) involves the activation of a topically or systemically delivered photosensitizing agent by light of a specific wavelength in the presence of oxygen. Methyl-aminolevulinic acid (ALA), the photosensitizer currently used in PDT, is preferentially absorbed by neoplastic tissue and converted into photoactive porphyrins. Sufficient time needs to be allowed for accumulation of porphyrins prior to exposure to a light source, usually red or blue light, with a wavelength corresponding to the excitation peaks of the photosensitizer. Cellular dysfunction and death results from the interaction of cellular components with the reactive oxygen species that are generated, resulting in tumor destruction.

### Efficacy

PDT has been shown to be effective for treating actinic keratosis and Bowen's disease [114], although evidence to support its use for treating invasive SCC is much less robust and there have been no RCTs that have included invasive SCCs.

Eleven small open-label studies have described the use of topical PDT to treat invasive SCCs, although there is much variation between them in terms of application time of photosensitizer, light source and dose employed, and total number of treatments [115–125]. Apparent initial complete response rates to topical ALA–PDT in the first few weeks after treatment were highly variable, ranging from 0 to 100%, although there were generally very few invasive SCCs in each study. Residual tumor was found on biopsy in two of 10 treated SCCs that clinically appeared to have responded to PDT [116]. Five of the studies assessed recurrence in those patients whose SCCs had appeared to respond to PDT initially. Whilst there were no recurrences in two of the studies (six patients in total)

during follow-up of 3–38 months [115,124], the remaining studies all reported poor long-term outcomes. Of 16 patients with apparently responsive SCCs, 11 (69%) recurred during 3–47 months follow-up, with an overall predicted disease-free rate of just 8% 36 months posttreatment [118]. An overall response rate (controlled by histology and long-term follow-up of up to 36 months) of 83% was calculated for “superficial” (less than 1 mm thick) SCCs and 33% for “nodular” SCCs [116]. A later study by the same author reported recurrence in six of 14 (43%) responsive invasive SCCs (Clark level II–IV), and in nine of 32 “microinvasive” SCCs (Clark level II) [117].

The use of systemic PDT has been assessed in three open-label trials. Two of the studies reported an initial apparent complete response for all of the 14 included invasive SCCs treated [126,127]. However, residual SCC was found in six of 32 posttreatment biopsies by Pennington *et al.* [128], and with more than 50% of treated SCCs recurring within 6 months after PDT and a lack of correlation between recurrence and the presence of residual tumor at the initial assessment, further recruitment into the trial was abandoned.

### Drawbacks

PDT is not recommended to treat invasive SCCs.

### Comment

There is currently insufficient evidence to support the routine use of topical or systemic PDT to treat invasive SCCs.

### Other treatments

Not all patients are amenable to surgical or radiological treatment, and such treatments may also not be ideal for patients with genodermatoses and immunosuppressed patients who may be afflicted with multiple skin tumors. Such patients have an unmet need for effective topical and systemic therapies, and as new insights into the

pathogenesis of NMSC emerge, the development of targeted therapies is becoming an exciting prospect.

The evidence of the effectiveness of topical and systemic agents that have been used to treat SCC is summarised in Table 32.1.

### Drawbacks

Prolonged treatment duration over weeks to months may render systemically administered regimes inconvenient for patients and decrease patient compliance with topical self-administered therapies. Many unanswered questions remain about optimal doses and the long-term efficacy and safety of these therapies. Not all SCCs express the primary targets (EGFR/VEGR) against which the newer molecular-based therapies are targeted, so may not benefit from such treatments, although identification of molecular markers in future studies may help to screen for those patients who are most likely to respond.

### Comment

Reports of the use of these other treatments is largely limited to case reports of patients with unresectable SCCs, and small numbers of advanced aggressive SCCs in studies which mostly include other types of NMSCs. As experience grows with the use of molecular targeted therapies in noncutaneous SCC, and as trials addressing their use in cutaneous SCCs expand, this is an area where the body of evidence is likely to develop in the future. However, the routine use of these therapies for primary nonmetastatic SCCs is not currently advocated.

### Implications for clinical practice

In considering the clinical scenario of a large perineural SCC on the temple of a middle-aged man, the choice of treatment will largely depend on the geographic medical options for a particular

**Table 32.1** Current evidence for the effectiveness of topical and systemic treatments for cutaneous SCC.

Treatment	Mechanism	Current evidence
Imiquimod (topical)	Immune response modifier	Limited evidence of efficacy for primary invasive SCCs – anecdotal reports in patients unsuitable for surgery [129–137]
5-FU (intralesional/topical)	Pyrimidine analogue	<i>Intralesional</i> 1ml/lesion per week for 6 weeks Multicenter open-label trial 95% clearance at 16 weeks (23 patients). Recurrence not assessed [138] <i>Topical</i> 70% superficial regression in XP patients with multiple facial SCCs ( $n = 10$ ), 80% of those biopsied had residual tumor in deep dermis [139] 79% complete clinical regression of 53 SCCs with no recurrences 1 year posttreatment [140]
Interferon-alpha (intralesional)	Cytokine	Multicenter open-label trial ( $n = 27$ ) 88.9% histological clearance. Recurrence not assessed [141] Retrospective series 61% CR ( $n = 28$ ), 1 recurrence of ear SCC at 4 years [142]
Cetuximab	EGFR inhibitor	Phase II trial 400mg/m <sup>2</sup> , then 250mg/m <sup>2</sup> per week for 6 weeks – 69% disease control at 6 weeks ( $n = 36$ unresectable head and neck cutaneous SCCs) [143] Case report – 400mg/m <sup>2</sup> , then 200mg/m <sup>2</sup> weekly plus $\gamma$ -irradiation for locally advanced inoperable SCC, regressed to surgically operable size by 8 months [144]
Gefitinib	EGFR tyrosine kinase inhibitor	Phase II trial – neoadjuvant gefitinib prior to definitive surgery and/or radiotherapy in 22 aggressive cutaneous SCCs – 45.5% response rate [145]
Erlotinib	EGFR inhibitor	Ongoing phase II trial [146]
Bevacizumab, sorafenib, sunitinib	VEGF inhibitors	No trials with cutaneous SCC, but phase II trials with SCC of the head and neck
Ingenol mebutate ( <i>Euphorbia peplus</i> sap)	Unknown	Phase I/II study 50% CR after mean f/u 15 months [147]

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; CR, complete response; XP, xeroderma pigmentosum; f/u, follow-up.



patient, the surgeon's preference, convenience to the patient, and cost. Surgical excision has the advantage of producing a tissue specimen in which the margins can be evaluated histologically using formalin-embedded tissue processing with special stains, and surgical repair would yield a much less obvious scar. ED&C and cryotherapy are inappropriate to treat high-risk SCC. MMS has the advantage that it provides horizontal sections that track the tumor along nerve branches, so that tumor can be cleared before surgical closure. MMS should be considered for this particular lesion because of its aggressive perineural spread seen on biopsy, its proximity to important functional and cosmetic structures in the face, and the technique's ability to achieve and document clear margins before a complex definitive repair.

### Key points

- Risk factors for the recurrence of cutaneous SCCs are the treatment modality, size larger than 2 cm, depth greater than 2 mm, poor histological differentiation, location on the ear or mucosal areas, perineural involvement, location within scars or chronic inflammation, previously failed treatment, and immunosuppression.
- The evidence base for the treatment of cutaneous SCC is poor.
- None of the commonly used procedures has been tested in rigorous RCTs for invasive SCC.
- Case series that have followed up patients with cutaneous SCC treated by surgical excision, MMS, ED&C, cryotherapy, or radiotherapy all suggest 3–5-year recurrence rates of 10% or less. SCCs on the lip and ear recur more commonly.
- Comparison of the recurrence rates between the major commonly used treatments is almost impossible, as the choice of treatment is probably based on the likelihood of success (for example, only people with small uncomplicated SCCs are treated with destructive rather than excisional techniques).
- Small, thin tumors less than 2 cm in diameter in noncritical sites may be treated by surgical excision with 4 mm margins, ED&C, or cryotherapy.
- Higher risk tumors require surgical excision or MMS.
- RCTs with adequate long-term follow-up are needed in order to inform clinicians about the relative merits of the various treatments currently used for people with SCC. Such trials will need to be large in order to exclude small but important differences, and they will need to accurately describe the sorts of people entered in terms of risk factors for recurrences. The follow-up period in such studies needs to be 5 years or longer.

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## CHAPTER 33

# Basal cell carcinoma

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## Background

### Definition

Basal cell carcinoma (BCC) is defined as a slow-growing, locally invasive malignant epidermal skin tumor, which mainly affects Caucasians [1].

### Incidence/prevalence

BCC (or rodent ulcer) is the most common malignant cutaneous neoplasm found in humans [2,3]. For example, over 30 000 new cases are reported each year in the UK. This is likely to be an underestimate because of inconsistencies in registration of BCCs at regional cancer registries [4]. Many registries only register a person's first skin cancer, thus further underestimating the real burden of the problem (Figures 33.1, 33.2, and 33.3).

The tumor may occur at any age, but the incidence of BCC increases markedly after the age of 40. The incidence of BCC appears to be increasing in younger people, probably as a result of increased sun exposure [5–7]. Cancer registry data from part of the Eastern Region of the UK were analyzed for two periods, 1981–1989 and 1989–2006, and reported incidence of BCC in those <30 years had increased by 145% during the period, corresponding to an average annual increase of 8.53% [8]. A sustained rise in the incidence of BCC has been documented using a validated register in South Wales, UK [3]. In the USA, the incidence of BCC has doubled approximately every 14 years [9], and similar changes have occurred in Australia [10].

### Etiology

Eighty-five percent of all BCCs appear on the head and neck region [11,12]. Risk factors are fair skin, tendency to freckle [13], degree of sun exposure [14–16], excessive sun-bed use, radiotherapy, phototherapy, male sex, and a genetic predisposition [17]. Nevoid BCC syndrome (Gorlin syndrome) is an autosomal-dominantly inherited condition characterized by developmental abnormalities and the occurrence of multiple BCCs. Mutations in patients with nevoid BCC syndrome have been found on the patched gene located on

chromosome 9, which appears to be crucial for proper embryonic development and for tumor suppression [18].

### Clinical patterns

As Figures 33.1, 3.2, and 33.3 show, clinical appearances and morphology for BCC are diverse. They include nodular, cystic, ulcerated (rodent ulcer), superficial, morpheic (scarring), keratotic, and pigmented variants. Nodular BCC is the most common type (60%) in the UK. However, in other countries such as Australia, superficial BCC is the most common type [19]. Eighty-five percent of all BCCs appear on the head and neck region [11,12], visible areas where a good cosmetic and functional result is important.

### Prognosis

Growth of BCC is a localized phenomenon in people with a competent immune system. BCCs tend to infiltrate surrounding tissues in a three-dimensional fashion through the irregular extension of finger-like outgrowths, which may not be apparent clinically [20,21]. If left untreated, or if inadequately treated, the BCC can cause extensive local tissue destruction, particularly on the face. Neglected cases may even infiltrate bone and deeper structures, such as the brain, and cause death [22]. Death from BCC is extremely rare, but may occur in neglected cases and/or those with major underlying immunosuppression. The clinical course of BCC is unpredictable. A BCC can remain small for years with little tendency to grow, it may grow rapidly, or it may proceed by successive spurts of extension of tumor and partial regression [23]. Histological subtype (infiltrative, micronodular, or morpheic patterns), initial diameter, and male sex have been shown to be the best independent predictors of BCC invasion [24]. It is unknown whether the phenotypic characteristics of people who present with clusters of BCCs or those who develop BCCs on truncal sites are also associated with increased growth once a BCC has established.

### Diagnostic tests

The diagnosis is usually made clinically, with histological confirmation being made at the time of the intended definitive treatment –



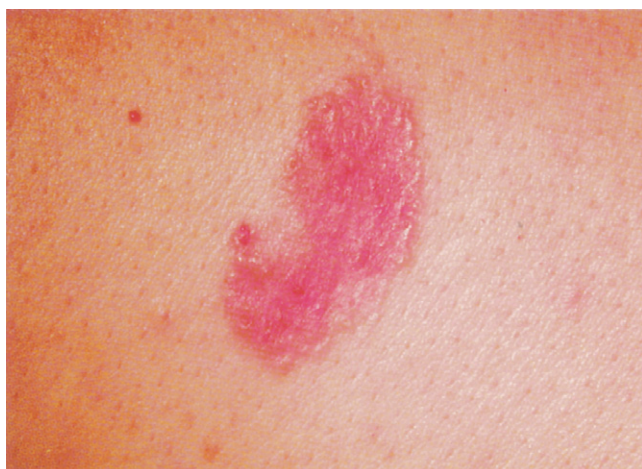


Figure 33.1 Superficial BCC.



Figure 33.3 A morpheic BCC.



Figure 33.2 A nodular BCC.

### Search methods

The following databases were searched up to the end of April 2012:

- Medline from 1966;
- Embase from 1980;
- The Cochrane Skin Group Specialized Trials Register;
- The Cochrane Library, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials;
- Mega Register of Controlled Trials on the Current Controlled Trials website and the National Research Register's Medical Research Council (MRC) Clinical Trials Directory.

The search strategy used to locate randomized controlled trials (RCTs) included search terms given in the *Cochrane Reviewers' Handbook* [25]. Search terms included: BCC, basal cell carcinoma, basal cell cancer, nodular BCC, nevoid BCC, Gorlin syndrome, rodent ulcer, Jacob's ulcer, basal cell epithelioma, basalioma, and nonmelanoma skin cancer (NMSC), including squamous cell carcinoma and BCC.

Prevention of skin cancer is discussed in Chapter 30.

often surgical removal. Diagnostic biopsies are usually performed before treatments such as radiotherapy.

### Aims of treatment

The three fundamental principles of treatment are to:

- eradicate the tumor;
- preserve function;
- produce an excellent or acceptable cosmetic result.

From a patient's perspective, the treatment should result in as little distress as possible in terms of pain, number of hospital visits, and scarring. From a health provider's perspective, it is important to balance efficacy against cost.

### Relevant outcomes

- Clearance of the lesion, as measured by absence of early treatment failure (within 6 months) and absence of long-term recurrence of the lesion measured at 3–5 years.
- Adverse effects in terms of atrophy, scarring, changes in pigmentation, and discomfort to the patient in terms of pain during treatment and afterwards.

### Questions

- What are the effective therapeutic interventions for BCC of the skin?
- How do the therapeutic interventions for BCC compare with each other?
- How do the cosmetic outcomes for these interventions compare?
- Are these interventions cost-effective?

The first-line treatment of BCC is often surgical excision with predetermined margins. Numerous alternatives are available, including curettage, cryosurgery, laser, excision under frozen-section control, Mohs micrographic surgery (MMS – the use of horizontal frozen sections and mapping to determine tumor clearance), radiotherapy, topical therapy, intralesional therapy, photodynamic therapy (PDT – the application of a cream to induce photodamage to the tumor using various light sources), immunomodulators (agents used to stimulate the immune system and work on eradicating the tumor), and chemotherapy. Surgical treatment requires access to a minor operating room, and most other treatments are carried out in specialist centers. Although there is wide variety in the treatment modalities used in the management

of BCC, and the vast majority of the tumors are probably treated successfully, little research is available that accurately compares these different treatment modalities. The evidence cited in the following summaries refers to RCTs unless specified otherwise.

### Surgical excision

Five RCTs were found that compared surgical excision with other interventions [26–31].

No RCTs have investigated the margin of excision that would be effective in the removal of BCC by surgical excision with predetermined margins. Proxy measures based on Mohs micrographic surgical margins required to remove BCCs, and histopathological studies of excised specimens have suggested that, for small nodular or superficial BCC, a 4 mm margin of normal skin will clear 95% of tumors [21,32]. Larger margins are required for tumors greater than 20 mm and for morpheic tumors [21].

### Surgery versus photodynamic therapy

These studies are covered under the PDT section.

### Surgical excision with frozen-section margin control

One RCT of 347 patients compared surgical excision and frozen-section margin control with radiotherapy in primary BCC less than 40 mm in diameter on the face [33]. As shown in Table 33.1, the main outcome measure was persistent or recurrent disease at 4 years. The secondary end point was the cosmetic result assessed by the patient, the dermatologist, and three persons not involved in the trial.

### Efficacy

The 4-year failure rate was 0.7% (95% confidence interval [CI], 0.1–3.9%) in the surgery group and 7.5% (95% CI, 4.2–13.1%) in the radiotherapy group. Cosmetic outcome as assessed by five observers over the 4 years of the study consistently favored surgery [34]. At 4 years, 87% of patients assessed their cosmetic results as good after surgery and 69% after radiotherapy.

### Potential drawbacks

After radiotherapy, dyspigmentations and telangiectasia developed in more than 65% of the patients at 4 years. Radiodystrophy affected 41% of the patients at 4 years.

### Comment

Concealment of allocation was clear and the paper showed evidence of an a priori sample size calculation; however, the analysis was conducted on a per-protocol basis. Several previous studies have reported good cure rates and cosmetic results with surgery and radiotherapy; however, the above study was the first randomized trial giving an unbiased comparison of the two treatments.

### Implications for practice

The trial shows that the failure rate was significantly lower in surgery than in radiotherapy for the treatment of BCC of the face for lesions less than 4 cm in diameter. Surgery may also be preferred for its cosmetic result.

### Mohs micrographic surgery

MMS is a technique in which 100% of the surgical margin is examined by mapping horizontal frozen sections from successive excision layers until clearance is achieved. A large case series of BCC treated with MMS found the recurrence rate at 5 years to be 1% [35]. One RCT compared MMS with conventional surgical excision for high-risk BCCs of the face [28].

### Surgical excision versus Mohs micrographic surgery

One RCT [28] of 374 patients with 408 primary lesions and 204 patients with 191 recurrent lesions compared MMS with surgery. As shown in Table 33.1, the primary outcome was recurrence and the secondary outcome was incomplete excision, suboptimal esthetic results, and excessive costs of treatment.

### Efficacy

**Primary basal cell carcinoma** Recurrence at 30 months did not differ significantly between the groups: five of 171 (3%) in standard excision versus three of 160 (2%) for MMS (difference 1%; 95% CI, –2.5 to +3.7%;  $P = 0.724$ ).

**Recurrent basal cell carcinoma** Recurrence at 18 months did not differ significantly between the groups: three of 93 (3%) in standard excision versus none of 95 after MMS (difference 3.2%; 95% CI, –2.0 to +5%;  $P = 0.119$ ). The overall esthetic outcome did not differ significantly between MMS and standard excision. Primary

**Table 33.1** RCTs evaluating surgical excision in the treatment of BCC.

Study	Method	Participants	Interventions	Outcomes	Notes
Avril <i>et al.</i> 1997 [33] (France)	Single center Randomization by sequential sealed envelopes ITT	HP BCCs T1: 174, T2: 173 patients Histological type T1: 79 N, 52 ulcerated, 36 S and pagetoid, 7 sclerosing; T2: 74 N, 50 ulcerated, 41 S and pagetoid, 8 sclerosing Location T1: 53 nose, 36 eyelids, 36 forehead, 10 chin, 5 ear; T2: 49 nose, 42 cheek, 35 eyelids, 29 forehead, 12 chin, 6 ear	T1: surgery – resection of whole tumor with a free margin of at least 2 mm from visible borders; T2: radiotherapy – interstitial brachytherapy, superficial contract therapy or conventional therapy, chosen by radiotherapist according to tumor parameters and location and patient characteristics	FU: 3, 6, 12 months after end of treatment; then yearly until fourth year Rate of histologically confirmed persistent tumor or recurrence after 4 years Patients examined by dermatologists; photographs of scar taken at three standardized distances	Ex: BCC on scalp or neck, patients who had total removal of BCC at biopsy, with 5 or more BCCs, life expectancy <3 years
Smeets <i>et al.</i> 2004 [28] (Netherlands)	Multicenter, telephone randomization	HP primary or recurrent BCC, 1 cm diameter, high risk or aggressive histopathological subtype. Primary T1: 198, T2: 199; recurrent T1: 102, T2: 102 patients	T1: MMS; T2: surgery	FU: recurrence at 18 and 30 months	ITT analysis

BCC, basal cell carcinoma; Ex, exclusion; FU, follow-up; HP, histologically proven; ITT, intention to treat; MMS, Mohs micrographic surgery; N, nodular; PP, per protocol; S, superficial.

BCCs had a significantly better esthetic outcome than recurrent BCCs ( $P = 0.038$ ), and cosmetic results became significantly poorer with increasing defect size for both primary ( $r = 0.383$ ,  $P < 0.001$ ) and recurrent BCCs ( $r = 0.351$ ,  $P = 0.001$ ). Total operative costs for both primary and recurrent BCCs are higher for MMS than standard excision ( $P < 0.001$ ).

### Potential drawbacks

Thirty-one primary BCCs (18%) and 31 recurrent BCCs (32%) were incompletely excised on first excision in the standard excision group. Primary tumors with aggressive histopathology were significantly more likely to be incompletely excised than those of the nonaggressive type. No adverse events were reported.

### Comments

Concealment of allocation was clear, and an intention-to-treat analysis was used.

It was suggested that the groups might not have been large enough for a significant difference to be detected. This study used 3 mm margins for both treatments to standardize the two treatment modalities (smaller margins are usually used for MMS). If standard excision was incomplete, a reexcision with a 3 mm margin was done. If the margins remained positive after the second excision, then MMS was undertaken.

Compared with surgical excision, the total treatment costs of MMS were significantly higher [36].

### Implications for practice

This is the only RCT comparing MMS with surgical excision for patients with high-risk facial BCCs. Treatment with MMS slightly, but not significantly, lowered the recurrence rate for both primary and recurrent BCCs in comparison with surgical excision. Five-year follow-up data are needed to determine definite recurrence rates in both groups. Almost a quarter of all aggressive carcinomas of 1 cm or more in diameter and about a third of all recurrent carcinomas were incompletely excised with a 3 mm margin, and

therefore MMS may well be preferable to use for these tumors to avoid larger defects, poor esthetic outcome, and functional problems.

One further RCT found that preoperative tumor curettage in MMS was associated with an increase in wound size [37].

### Cryotherapy

Three RCTs were found and are summarized in Table 33.2.

### Cryotherapy versus radiotherapy

One study of 93 patients compared radiotherapy with cryotherapy for primary BCC, excluding lesions on the nose or pinna [38]. The aims of the study were to compare the control of the tumors with the two treatments, to assess the final cosmetic result, and to compare the discomfort and inconvenience experienced by the patient. Cryotherapy consisted of two freeze-thaw cycles, freezing for 1 min each time.

### Efficacy

Recurrence rates at 1 year were 4% (two of 49) in the radiotherapy group and 39% (17 of 44) in the cryotherapy group. At 2 years, no further tumors had recurred in either group. The cosmetic results for the two modes of treatment were not significantly different.

### Potential drawbacks

The degree of pain, discomfort, discharge, and bleeding from the treated areas was the same in both groups. Only one patient from each group was seriously inconvenienced by the treatment. Hypopigmentation was more common than hyperpigmentation with both modes of treatment (81% of those in the radiotherapy group and 88% of those in the cryotherapy group). Seven patients treated with radiotherapy developed some radiation telangiectasia. Hypopigmentation and telangiectasia tend to be lifelong. Five patients treated with cryotherapy developed milia, which all disappeared by 1 year.

**Table 33.2** RCTs evaluating cryotherapy in the treatment of BCC.

Study	Method	Participants	Interventions	Outcomes	Notes
Hall <i>et al.</i> 1986 [38] (UK)	Single center Method of randomization not known, PP	105 patients BP BCCs T1: 44; T2: 49 patients Sites: T1: 30 neck and face, 6 eyelids, 8 trunk; T2: 40 neck and face, 3 eyelids, 6 trunk	T1: cryotherapy using a Cry-Owen liquid-nitrogen spray gun; all lesions treated with two freeze-thaw cycles, freezing for 1 min each time, with a thaw time of at least 90 s; T2: radiotherapy (130 kV X-rays)	FU: recurrence of tumor and cosmetic appearance at 1, 6, 12, 24 months after treatment Tumor identified histologically	12 excluded: 5 died of other causes, 7 lost to FU Ex: recurrent tumors, lesions on nose or pinna, lesion near eye and vision in eye <6/18
Mallon and Dawber, 1996 [39] (UK)	Single center Method of randomization not known, PP	84 patients Mostly clinically proven BCCs Facial lesions $\leq 1.5$ cm not extending >3 mm below skin were included. T1: 36; T2: 48 patients Mean age T1: 67; T2: 69 years	T1: single 30 s freeze-thaw cycle T2: double 30 s freeze-thaw cycle	FU: T1: 10 months to 7.1 years; T2: 1.2–6.1 years Lesions assessed clinically	7 lost to FU, T1: 2, T2: 5
Thissen <i>et al.</i> 2000 [40] (Netherlands)	Single center Method of randomization not known, PP	103 patients Some BP BCCs Lesions S or N, <2 cm diameter, localized anywhere on the head and neck	T1: surgery T2: cryosurgery (no. 3 curette used to debulk the tumor; no. 1 used to remove remainder of BCC around the borders. Freezing: two freezing periods, each lasting 20 s)	FU: cosmetic and recurrence at 1 year Recurrence assessed clinically	Lost to FU: 3 in control group did not turn up for visits, 1 died (unrelated to treatment), 3 developed recurrent BCC (all T2)

BCC, basal cell carcinoma; BP, biopsy-proven; Ex, exclusion; FU, follow-up; HP, histologically proven; N, nodular; PP, per protocol; S, superficial.



**Comments**

The concealment of allocation was unclear, and the analysis was conducted on a per-protocol basis. There was no indication of the type of lesion.

**Implication for clinical practice**

Cryotherapy, although convenient and less expensive than radiotherapy, does not appear to have better cure rates than radiotherapy (especially for lesions >2 cm). Cosmetic effects for radiotherapy and cryotherapy are comparable. Variations in technique occur between different physicians and may account for differences in outcome. Lesions larger than 2 cm in diameter treated by cryotherapy recurred, but lesions larger than 2 cm and treated with radiotherapy were controlled. It was concluded that cryotherapy does not offer a satisfactory alternative to radiotherapy in the treatment of BCC.

**Cryotherapy: varying number of freeze–thaw cycles**

In a second RCT of 84 patients, one freeze–thaw cycle of 30 s was compared with two freeze–thaw cycles of 30 s for low-risk facial BCCs [39].

**Efficacy**

Recurrence rates were significant: 4.7% with two freeze–thaw cycles and 20.6% with one cycle after a median of 18 months.

**Potential drawbacks**

No mention was made of adverse effects of the treatment.

**Comments**

Concealment of allocation was unclear, and the analysis was conducted on a per-protocol basis. Only common facial lesions of 1.5 cm or less were included, and not all of the lesions were biopsied. Variations in technique between different physicians may account for differences in outcome.

**Implications for clinical practice**

Facial lesions require a double freeze–thaw cycle with liquid nitrogen if the high cure rates in many reports of formal excision or radiotherapy are to be achieved. Although case series suggest that higher clearance rates can be achieved, particularly with low-risk tumors, more prospective evidence is required.

**Cryotherapy versus surgical excision**

A third RCT of 96 patients [40] compared cryosurgery with surgical excision for BCC of the head and neck. The primary outcome was the cosmetic result, but recurrence rates in both groups were also compared. Recurrences were treated by surgical excision. Cosmetic results were judged by five independent professional observers and by the patients.

**Efficacy**

The recurrence rate for cryosurgery was three of 48 at 1 year, whereas in the surgery group no recurrences developed at 1 year. The cosmetic results after surgical excision generally received a significantly better evaluation in comparison with cryosurgery for superficial and nodular subtypes localized in the head/neck region.

**Comments**

Concealment of allocation was unclear. The analysis was conducted on a per-protocol basis, although the paper showed evidence of an a priori sample size calculation.

**Potential drawbacks**

Two patients (4%) developed secondary wound infections in the first and second weeks after surgery, for which systemic antibiotics were given. Ninety percent of the patients in the cryotherapy group complained of moderate to severe swelling of the treated area, followed by long-lasting leakage of exudates from the defect. After cryotherapy, three patients (6%) had secondary wound infection, for which systemic antibiotics were given.

**Implications for clinical practice**

Surgical excision for nodular and superficial lesions smaller than 2 cm is cosmetically more acceptable than cryosurgery. Cryotherapy does not appear to be a satisfactory alternative to surgery for superficial or nodular lesions in the head and neck area of less than 2 cm in diameter.

**Photodynamic therapy**

PDT is a nonionizing radiation treatment modality. It uses the interaction between visible light and tumor-sensitizing agents to generate cell death.

**Methyl aminolevulinate photodynamic therapy versus placebo**

Two multicentre RCTs, performed in Australia and the USA, with short follow-up periods of just 3 and 6 months, compared methyl aminolevulinate (MAL)–PDT with placebo [41], summarized in Table 33.3.

**Efficacy**

The results for the histologically verified lesion complete response rates were higher with MAL–PDT compared with placebo (73% (55/75) versus 27% (20/75)). Cosmetic outcome was good or excellent in 98% of evaluable, completely responding lesions treated with MAL–PDT.

**Methyl aminolevulinate photodynamic therapy versus 5-aminolevulinate photodynamic therapy**

Two studies [42,43] compared two topical photosensitizers, 5-aminolevulinate (ALA) and MAL.

**Efficacy**

The first study [42] randomized 43 nodular BCC to either ALA–PDT or MAL–PDT. Most tumors were debulked prior to PDT.

There was no significant difference in terms of clearance or pain scores between the two groups at 8 weeks after treatment; however, the cost of MAL–PDT was found to be sixfold higher compared with ALA–PDT.

The second study randomized 24 patients with 112 superficial BCCs to either ALA–PDT or MAL–PDT [43] and illuminated with a diode laser. There was no significant difference in lesion clearance at 12 weeks when ALA–PDT (44/72) was compared with MAL–PDT (23/40) ( $P = 0.9$ ).

Tumors were debulked prior to PDT.

**Photodynamic therapy versus surgery**

Four RCTs compared PDT with surgery [26,27,29–31], and these are summarized in Table 33.3.

The first RCT of 103 patients compared surgical excision versus MAL–PDT in primary nodular BCC of the face [26,27].

**Efficacy**

The response at 3 months was 98% for surgery versus 91% for PDT, difference 4.8% (95% CI, –3.4 to +13%). There was no significant



**Table 33.3** RCTs evaluating photodynamic therapy in the treatment of BCC.

Study	Method	Participants	Interventions	Outcomes	Notes
Wang <i>et al.</i> 2001 [45] (Sweden)	Single center Randomized according to a stratified randomization pattern in blocks of 10 patients, PP	HP BCC 44 women; 44 men; age range 42–88 years Type: T1: 22 S, 25 N; T2: 17 S, 24 N Distribution: 47 trunk, 25 head and neck, 10 legs, 6 arms	T1: PDT (20% weight-based ALA/ water-in-oil cream applied to lesion; irradiation 6 h later T2: cryosurgery (2 freeze–thaw cycles)	FU: 1, 4, 8 weeks, 3 months after treatment Last FU 12 months after first treatment Punch biopsy at 3 and 12 months	Ex: BCC on nose; M growth; porphyria; abdominal pain of unknown etiology; photosensitivity; treatment of BCC with topical steroids type III or IV within the last month
Soler <i>et al.</i> 2000 [48] (Norway)	Single center Randomization numbers in locked envelopes. The patients were randomly allocated on the treatment day to one of the two arms in blocks of four patients, ITT	HP BCC 83 patients 245 lesions	All lesions in both groups topical 20% ALA, removed after 3 h and light source applied T1: laser light (630 nm); T2: broadband light	FU: 3, 6 months after treatment Outcomes: complete, partial, or no response; cosmetic outcome and pain intensity during treatment and FU	
Foley <i>et al.</i> 2009 [41] (Australia, USA)	Two multicenter studies (similar design) Computer-generated randomization and stratified by center	HP N BCC, $n = 131$ (160 lesions) ( $\leq 5$ mm depth)	T1: MAL–PDT; T2: placebo. Surface debridement prior to treatment. MAL or placebo applied to lesion for 3 h and covered with an adhesive occlusive dressing. Wavelength, 570–670 nm; light dose, 75 J/cm <sup>2</sup> ; light intensity, 50–200 mW/cm <sup>2</sup>	FU: 3 and 6 months	Blinded outcome assessor
Lui <i>et al.</i> 2004 [49] (Canada)	Multicenter Method of randomization not given	54 patients (421 BP N or S BCC or Bowen disease) Age range 22–79 years, mean 55	Single i.v. infusion of 14 mg/m <sup>2</sup> of verteporfin followed 1–3 h later by 60, 120 or 180 J/cm <sup>2</sup>	FU: 6 months (biopsy-proven)	7 patients (51 tumors) lost to FU. Analysis PP
Basset-Seguin 2008 (Europe)	Multicenter, open randomized study Method of randomization not given. Analysis PP	118 patients (219 lesions) with S BCCs. T1: 60; T2: 58 patients. T1: gentle removal of surface prior to PDT	T1: MAL–PDT; T2: cryo (double freeze–thaw)	FU: 3, 12, 36 months	Abstract
Mosterd <i>et al.</i> 2008 [29] (Europe)	Randomization per tumor using a computer-generated random allocation scheme	149 patients (173 lesions) with N BCCs. T1: 85; T2: 88 lesions	T1: ALA–PDT; T2: SE (3 weeks prior to PDT a partial debulking under local anesthesia)	FU: 3, 6, 12, 18 months and 2, 3, 4, and 5 years	
Szeimies <i>et al.</i> 2008 [30] (Europe, Australia)	Multicenter, noninferiority study	196 patients (1.4 S BCC/ patient). T1: 100; T2: 96 patients	T1: MAL–PDT; T2: SE	FU: 3, 6, and 12 months	
Schleier <i>et al.</i> 2007 [43] (Germany)	Single center. Method of randomization not known Patient and therapist blinded to treatment	24 patients (112 lesions) with HP S BCC. T1: $n = 13$ ; T2: $n = 11$	T1: ALA–PDT; T2: MAL–PDT Treated for 3 h and then illuminated with a diode laser	FU: 12 weeks and 6 months (clinical examination)	
Kuijpers <i>et al.</i> 2006 [42] (Netherlands)	Single center Patients were blinded Method of randomization not known	N BCC anywhere on skin and periocular area and hairy scalp with clinical diameter $< 20$ mm. T1: $n = 22$ ; T2: $n = 21$	T1: ALA–PDT; T2: MAL–PDT Tumors debulked prior to PDT	FU: 8 weeks	
Arits <i>et al.</i> 2010 [47] (Netherlands)	Method of randomization not known. Stratified by patient age and tumor location	453 patients with S BCC T1: $n = 118$ ; T2: $n = 121$ ; T3: $n = 125$	T1: PDT; T2: imiquimod; T3: 5-FU	FU: 3 and 12 months	
Berroeta <i>et al.</i> 2007 [31]	Random allocation list generated by computer. Random allocations concealed in opaque envelopes. No blinding. Analysis ITT	31 patients with 40 N BCCs ( $< 2$ cm)	T1: ALA–PDT; T2: SE Superficial curettage before PDT treatment	FU: 3, 6, and 12 months	
Rhodes <i>et al.</i> 2004 and 2007 [26,27] (UK)	Multicenter, phone/fax randomization	HP, N BCC, T1: 52; T2: 49 patients (110 lesions)	T1: MAL–PDT (75 J/cm <sup>2</sup> red light (570–670 nm); T2: surgery (with 5 mm margin)	FU: clinical clearance at 3, 12 months after treatment. Cosmetic outcome at 3, 12 months. Cosmesis and lesion recurrence at 24 months and 5 years	Ex: high-risk BCC on face. 24% of lesions were retreated. Analysis PP

ALA, aminolevulinic acid; BCC, basal cell carcinoma; BP, biopsy-proven; Ex, exclusion; FU, follow-up; HP, histologically proven; ITT, intention to treat; M, morphea-like; MAL–PDT, methyl aminolevulinate photodynamic therapy; MMS, Mohs micrographic surgery; N, nodular; PDT, photodynamic therapy; PP, per protocol; S, superficial.

difference in clearance at 12 months (98% for surgery vs 85% for PDT) ( $P = 0.15$ ). At 5 years after last treatment, the sustained lesion complete response rate, estimated by the complementary log-log model, was 76% (95% CI, 59–87%) for MAL-PDT compared with 96% (95% CI, 84–99%) for surgery, per-protocol population ( $P = 0.01$ ). The cosmetic outcome was significantly better at 12 and 24 months on the patients' assessment and at 3, 12, and 24 months on investigator evaluation ( $P < 0.001$ ). Cosmetic outcome at 5 years was significantly better for MAL-PDT compared with surgery as assessed by the investigator ( $P = 0.007$ ) [27].

#### **Potential drawbacks**

Significantly more patients treated with MAL-PDT compared with those treated with surgery reported adverse events (52% vs 29%;  $P = 0.03$ ). Most of the adverse events were transient local reactions commonly associated with PDT, such as a burning sensation on the skin, pain in the skin, or erythema.

#### **Comments**

Concealment of allocation was clear, but the analysis was per-protocol. Lesions with an incomplete response to PDT at 3 months received a second treatment cycle and were evaluated 3 months later.

#### **Implications for clinical practice**

Long-term follow-up indicates superior efficacy of surgery to MAL-PDT in nodular BCC. There is a trend toward higher recurrence rates with PDT in comparison with surgery, and significantly more patients reported adverse events in the PDT group. However, PDT may be preferred for its cosmetic results.

#### **Efficacy**

The second RCT [29] compared fractionated ALA-PDT with surgery in 173 primary nodular BCCs. A 3-year interim analysis revealed cumulative incidence of failure as 2.3% for surgical excision and 30.3% for PDT ( $P = 0.001$ ).

The third RCT [30] was a noninferiority study of MAL-PDT versus surgery in 196 patients with primary superficial BCC. Clearance at 3 months for superficial BCC was 92.2% for MAL-PDT compared with 99.2% for surgery, confirming the noninferiority hypothesis. At 12 months, 9.3% of the lesions recurred in MAL-PDT compared with none in the surgery group. Cosmetic outcome was statistically superior for MAL-PDT at all times.

The fourth study [31] randomized 31 patients with 40 nodular BCC to ALA-PDT or surgery. There was no significant difference in number of lesions that cleared at 1 year (13/21 ALA-PDT vs 15/19 surgery). PDT was significantly more painful than surgery during treatment (median pain 5/10 for PDT vs 0/10 for surgery,  $P = 0.24$ ). There was no significant difference in cosmetic outcome. Although not statistically significant, there were no persistent BCCs in the surgery group, but five lesions persisted in the PDT group.

#### **5-Aminolevulinic photodynamic therapy versus laser versus laser plus 5-aminolevulinic photodynamic therapy**

One study [44] compared ALA-PDT versus YAG laser ablation versus YAG laser ablation plus ALA-PDT for recurrent nodular BCC.

#### **Efficacy**

Combination therapy demonstrated the most effective treatment at all time points, with a final efficacy of 98.97% versus 94.85% (PDT

only) and 91.75% for YAG laser only. The combination therapy also gave the best esthetic results.

#### **Photodynamic therapy versus cryotherapy**

One RCT of 88 patients compared PDT with cryotherapy with two freeze-thaw cycles for BCC [45].

#### **Efficacy**

There was no significant difference in recurrence rates at 12 months, and both were quite high. Histological recurrence rates at 1 year were 25% (11 of 44) in the PDT group, compared with 15% (six of 39) in the cryotherapy group, despite multiple retreatments in the PDT group. Scarring and tissue defects scored significantly better following PDT.

A second study of 118 patients [46] compared MAL-PDT versus cryotherapy for superficial BCC. Cumulative recurrence rates at 5 years follow-up was 22% (22/100) in MAL-PDT and 20% (19/93) for cryotherapy ( $P = 0.86$ ). Recurrence at 1 year was 8% (eight of 97) in the PDT group, compared with 16% (15 of 91) in the cryotherapy group. At 36 months, the estimated complete response rate was 74% for both groups. More people had an excellent cosmetic outcome with MAL-PDT than with cryotherapy at 5 years (56% (18/32) versus 14% (6/43);  $P = 0.00078$ ).

#### **Potential drawbacks**

In the first study, more patients indicated pain and discomfort during and after treatment with PDT, but the differences were not statistically significant.

#### **Comments**

For the first study, concealment of allocation was clear. For both studies, the analysis was conducted on a per-protocol basis and no sample size calculation was given.

#### **Implications for clinical practice**

Although tolerability for patients was greater and cosmetic outcomes were considered better in the PDT group, the published efficacy data to date support the use of PDT for superficial BCC but do not support the introduction of PDT for the treatment of nodular BCC. Further studies demonstrating greater efficacy are needed, and follow-up periods for outcome assessment should be 3–5 years.

#### **Photodynamic therapy versus imiquimod versus 5-fluorouracil**

One study (abstract) [47] randomized 453 patients with 453 superficial BCC to PDT, imiquimod, or 5-fluorouracil (5-FU).

#### **Efficacy**

Interim analysis indicate that all three modalities are almost equally effective with a good cosmetic result. Treatment failure at 3–12 months occurred in 12% (5/42) in the PDT group, 5% (3/56) in the imiquimod group and 6% (3/51) in the 5-FU group. At 3 months, 66% in the PDT group, 62% in the imiquimod group, and 53% in the 5-FU group had good to excellent cosmetic results.

#### **Laser versus broadband halogen light**

Another RCT [48] of 83 patients compared the clinical and cosmetic outcomes of superficial BCCs using either laser or broadband halogen light in PDT with topical ALA.

### Efficacy

At the end of the study (6 months), 86% in the laser group and 82% in the broadband halogen group were evaluated as having complete responses by both investigators. The study showed no significant differences in the cure rate ( $P = 0.49$ ; 95% CI,  $-7$  to  $+14\%$ ) or cosmetic outcome ( $P = 0.075$ ) between light exposure from a simple broad lamp with continuous spectrum (570–740 nm) or from a red-light laser (monochromatic 630 nm).

### Potential drawbacks

Eighty-three percent of patients receiving PDT with laser light and 76% of those receiving PDT with broadband halogen light reported some discomfort during and after illumination. Sixty-eight percent of the patients who received laser light and 74% of the patients who received broadband halogen light reported some degree of discomfort (stinging, itching, pain, headache, sensation of warmth, or blushing) during the first week of treatment. No serious adverse events were reported during the 6-month follow-up.

### Comments

Although 83 patients were involved, 245 superficial BCCs were included in the study, indicating more than one lesion per patient. Concealment of allocation was clear, and analysis was carried out on an intention-to-treat basis; however, no sample size calculation was included.

### Implications for practice

The results show that topical ALA-based PDT with a broadband halogen light source gives short-term (6 months) cure rates and a cosmetic outcome similar to those obtained with a laser light

source, although both are considerably inferior to excisional surgery. Reduced costs, increased safety, and the possibility of general use by dermatologists are other elements in favor of the lamp as a suitable light source.

### Verteporfin and red light: a dose-ranging study

One RCT [49] compared three different light doses in 54 patients with 421 multiple BCCs and found a dose response for histological clearance 6 months after treatment (nodular BCC 76–100% and superficial BCC 63–97%) (Table 33.3).

### Implications for practice

There is a need for long-term follow-up in order to identify the correct light dose, balancing response and cosmetic appearance.

### Intralesional interferon therapy

Interferons are naturally occurring glycoproteins that exhibit antiviral, antitumor, and immunomodulatory activities. Four RCTs were found (Table 33.4).

### Interferon alfa-2a and/or -2b

#### Efficacy

In the first trial [50], 45 patients were randomly assigned to receive 15 or 30 million units of interferon alfa-2a or -2b, or both interferon alfa-2a and -2b. The aim of the study was to evaluate the effectiveness of the interferons alone and whether this effect might be increased by their combination. The complete response at 8 weeks was similar, at 66–73% in each treatment group. No significant differences were found between the groups in this respect.

**Table 33.4** RCTs evaluating intralesional interferon in the treatment of BCCs

Study	Method	Participants	Interventions	Outcomes	Notes
Alps et al. 1996 [50] (Turkey)	Single center Method of randomization not known ITT	45 patients HP BCC T1: 15; T2: 15, T3: 15 patients Mean age T1: 58.7, T2: 63.6, T3: 60.3 years Histological types T1: 12 N, 1 S, 2 M; T2: 11 N, 2 S, 2 M; T3: 11 N, 2 S, 2 M	T1: INF alfa-2a; T2: INF alfa-2b; T3: INF alfa-2a and -2b	FU: cytologic specimens taken 8 weeks after completion of therapy; all cases evaluated clinically and histologically	Ex: Recurrent lesions, genetic or nevus conditions, deep tissue involvement
Cornell et al. 1990 [51] (USA)	Multicenter (4) Randomization by computer-generated PP	T1: 123; T2: 42 patients BP BCC Mean age T1: 56; T2: 57 years Histological type T1: 57 S, 66 N ulcerative; T2: 19 S, 23 N	T1: intralesional injections 1.5 million IU IFN alfa-2b; T2: vehicle for IFN preparation 3 alternate days/week for 3 consecutive weeks	FU: weekly after each of the three treatments. then at 5, 9, 13 weeks after completion of treatment, then every 3 months to 52 weeks	Ex: Previously received therapy to test site, immunosuppressive or cytotoxic therapy (within previous 4 weeks), or exogenous IFN/IFN alfa-2b (Intron A), debilitating illness, lesion in perioral or central area of the face or penetrating to deep tissue
Edwards et al. 1990 [52] (USA)	Single center Method of randomization not known, PP	T1: 33; T2: 32 patients BP BCC Age range 35–65 years Histological type T1: 16 S, 17 N; T2: 15 S, 15 N	10 million IU zinc chelate IFN alfa-2b; T1: single injection; T2: one dose per week for 3 weeks	BCC measured, photographed before each treatment and at beginning of weeks 2, 8, 12, and 16 after the first injection Biopsy at week 16	Ex: thromboembolic disease, radiation therapy to the test site area, history of arsenic ingestion, pregnancy, immunosuppression, receiving nonsteroidal anti-inflammatory drugs, M BCC, recurrent cancers, deeply invasive lesions, periorificial tumors, central facial BCC
Rogozinski et al. 1997 [53] (Poland)	Single center Method of randomization not known, ITT	T1: 17; T2: 18 patients	T1: recombinant INF beta; T2: placebo	FU: 16 weeks after treatment and 2 years	

BCC, basal cell carcinoma; BP, biopsy-proven; Ex, exclusion; FU, follow-up; HP, histologically proven; IFN, interferon; M, morphea-like; N, nodular; PP, per protocol; S, superficial.

**Potential drawbacks**

One drawback is pain at the injection site. All patients had flu-like syndrome (fever, chills, headaches, fatigue, myalgia), especially within the first 2 weeks after the initiation of interferon therapy.

**Comments**

Concealment of allocation was unclear; however, the analysis was performed on an intention-to-treat basis.

**Implications for clinical practice**

Combining interferon alfa-2a and -2b does not appear to increase their effectiveness.

**Interferon alfa-2b versus vehicle**

Another trial of 165 patients [51] compared interferon alfa-2b at 1.5 million units three times weekly for 3 weeks with vehicle in a 3:1 ratio of interferon-treated to placebo-treated patients.

**Efficacy**

Eighty-one percent of interferon-treated patients were clinically and histologically cured at 52 weeks, compared with 20% of the placebo recipients. The cure rate was independent of lesion type or size.

**Potential drawbacks**

Flu-like symptoms occurred more commonly in the interferon-treated group.

**Comments**

Concealment of allocation was clear; however, the analysis was conducted on a per-protocol basis. Interestingly, 20% of the patients treated with vehicle appeared to have a histological cure at 1 year. Longer term studies are needed to determine whether this is genuine.

**Implications for clinical practice**

Interferon alfa-2b has not been compared with current standards of surgical or radiotherapy cures and so cannot be recommended as a first-line therapy. Interferon alfa-2b could be considered for patients who are not candidates for simple surgery or who desire nonsurgical therapy.

**Number of dosages of interferon alfa-2b**

A third RCT [52] compared a single dose of 10 million IU pro-tamine zinc chelate interferon alfa-2b (a sustained-release preparation) with the same dose weekly for 3 weeks in 65 patients. Histological cure rates at 16 weeks were 52% and 80% for one and three doses weekly, respectively, and the cosmetic effect was graded as excellent by 51% of the patients. Side effects were similar for both the single-dosage and repeated-dosage groups, and were those common to interferon (Table 33.4).

**Implications for clinical practice**

Refinement of the formulation to improve the release of interferon in order to help minimize side effects has not been realized. A trial is needed to compare the sustained-release formulation of interferon alfa-2b with standard interferon alfa-2b.

**Interferon beta**

Recombinant interferon beta at 1 million units three times weekly for 3 weeks has been compared with placebo in a trial of 35 patients [53].

**Efficacy**

After 2 years of follow-up, 47% of patients in the treatment group showed a complete response, compared with none in the placebo group.

**Potential drawbacks**

Inflammation at the injection site was found in 11 of the 16 patients in the treatment group and four of the 18 receiving placebo.

**Comment**

The analysis was conducted on a per-protocol basis; concealment of allocation is not known.

**Implications for clinical practice**

The paper suggests recombinant interferon beta as an alternative treatment for BCC. The response rate at 47% is too low for it to be recommended as a treatment for BCC.

**BEC-5 cream**

BEC-5 is a mixture of 0.005% solasodine glycosides found in solanaceous plants (aubergine). BEC-5 cream binds to endogenous ectins and shows preferential cytotoxicity to human cancer cells.

In a double-blind randomized trial, BEC-5 cream was compared with matching vehicle [54] (Table 33.5). Biopsy-proven lesions, excluding morpheic BCC, were treated twice daily under occlusion with BEC-5 or vehicle for 8 weeks.

**Efficacy**

At 8 weeks, significantly more tumors cleared in the BEC-5 group compared with the vehicle group (66% (41/ 62) vs 25% (8/32);  $P = 0.001$ ) The cure rates after 1 year were also significantly different: 52% (32/62) in the BEC-5 group and 16% (5/32) in the placebo group.

**Potential drawbacks**

There were no major treatment-related adverse effects.

**Comment**

Concealment of allocation was unclear, and the analysis was conducted on an intention-to-treat basis.

**Table 33.5** RCTs evaluating BEC-5 in the treatment of BCC.

Study	Method	Participants	Interventions	Outcomes	Notes
Punjabi <i>et al.</i> 2008 [54] (UK)	Multicenter method of randomization not known	94 patients BP BCC Age 32–95 years	T1: BEC-5; T2: vehicle; twice daily under occlusion for 8 weeks	Patients reviewed every 2 weeks Repeat punch biopsy at 8 weeks in 84 patients	10 patients in T1 did not complete the study

BCC, basal cell carcinoma; BP, biopsy-proven.



**Implications for clinical practice**

Although significant differences were found between the groups, the cure rate is not sufficiently high in comparison with other treatments for this method to be recommended.

**PEP005 (ingenol mebutate) gel**

A dose-finding phase IIa study [55] randomized 60 patients with superficial BCC to two different treatment regimens for ingenol mebutate gel – and within each arm, different concentrations of ingenol mebutate gel or vehicle.

**Efficacy**

Efficacy appeared to be dose related. Overall, complete clinical and histological lesion clearance rates were highest with ingenol mebutate gel, 0.05%. Further studies need to be undertaken.

**5-Fluorouracil applied topically**

The primary mechanism of action of 5-FU is thought to be inhibition of DNA synthesis by competitive inhibition of thymidylate synthetase [56].

**5-Fluorouracil in phosphatidylcholine versus 5-fluorouracil in petrolatum**

A double-blind randomized pilot study [57] of 5-FU 5% cream in phosphatidylcholine (PC) vehicle was compared with 5-FU 5% in petrolatum. Further details of this study are given in Table 33.6. PC was used as a vehicle to facilitate the penetration of 5-FU.

**Efficacy**

Histological cure at week 16 was 90% with the PC vehicle and 57% with the petrolatum-based cream. The patients also evaluated the treatment site on each visit for cosmetic appearance. No differences were detected in the clinical appearance or adverse effects between the two therapeutic arms of the study.

**Comments**

The study was not adequately powered to detect any statistically significant differences in outcome between the groups, and concealment of allocation was unclear; however, the analysis was conducted on an intention-to-treat basis.

**Potential drawbacks**

Local irritation, erythema, ulceration, and tenderness were common reactions, but were well tolerated by the patients. Minimal itching and discomfort were experienced by some of the patients in both treatment arms.

**Implications for clinical practice**

The study may indicate an increase in short-term eradication of BCC using a PC-based vehicle in comparison with conventional petrolatum-based formulations of 5-FU. There was an excellent cosmetic outcome in all treatment sites before excision at week 16. Further large-scale double-blind trials with long-term follow-up periods of 3–5 years are needed to establish the efficacy of this treatment modality.

**5-Fluorouracil–epinephrine injectable gel**

An open-label randomized study of 122 patients [58] tested the safety, tolerability, and efficacy of six treatment regimens of 5-FU–epinephrine gel. Two doses and four treatment schedules were used (Table 33.6).

**Efficacy**

Overall, the average response rate for the six regimens was 91%, as defined by the absence of any tumor on the basis of histological analysis of excised specimen. A 100% complete response rate was observed in patients who received 5 mL 5-FU–epinephrine gel twice weekly for 4 weeks – a 92% response rate for superficial lesions and a 91% response rate for nodular lesions.

All regimens appeared to work well and there were no statistically significant differences between them. The various treatment regimens with higher doses and/or treatment frequency resulted in higher complete response rates than obtained in an earlier pilot study [59]. The cosmetic appearance of the lesion site prior to excision at 3 months ranged from good to excellent.

**Potential drawbacks**

All patients had transient, moderate to severe stinging, burning, or pain at the time of injection. Local tissue reactions were confined to the treatment site and included erythema, swelling, desquamation, erosions, and eschar in most patients. Hyperpigmentation was

**Table 33.6** Randomized controlled trials evaluating 5-fluorouracil (5-FU) in the treatment of basal cell carcinoma.

Study	Method	Participants	Interventions	Outcomes	Notes
Romagosa <i>et al.</i> 2000 [57] (USA)	Single center Method of randomization not known ITT	13 patients, 17 BP non-S BCCs $\geq 0.7$ cm greatest diameter	T1: 5% 5-FU in PC vehicle T2: 5% 5-FU in petrolatum base Applied a.m. and p.m. for 4 consecutive weeks	FU: every 4 weeks for 16 weeks Final visit was biopsy of site	Ex: systemic disease, women of childbearing age, facial BCCs
Miller <i>et al.</i> 1997 [58] (USA)	Multicenter, randomized, open-label Method of randomization not known PP	97 males, 25 females Single BP BCC Mean age 61 years Histological type: 38 S, 85 N Location: 9 head, 9 neck, 38 upper extremities, 11 lower extremities, 55 trunk Lesion area median 80 mm <sup>2</sup>	6 treatment regimens with 5-FU/epi gel: T1: 1.0 mL once weekly for 6 weeks; T2: 0.5 mL once weekly for 6 weeks; T3: 1.0 mL twice weekly for 3 weeks; T4: 0.5 mL twice weekly for 3 weeks; T5: 0.5 mL twice weekly for 4 weeks; T6: 0.5 mL three times weekly for 2 weeks	FU examinations of patients at 1, 4, 8, 12 weeks after last injection At each visit, patient and investigator gave subjective evaluation of cosmetic appearance of lesion	Ex: high-risk sites. Lesions with deep tissue involvement, basal cell nevus syndrome, hypersensitivities or allergies to 5-FU, sulfites, epinephrine, bovine collagen, history of autoimmune disease, pregnancy. Six patients were lost to follow-up

BCC, basal cell carcinoma; BP, biopsy-proven; Ex, exclusion; FU, follow-up; 5-FU, 5-fluorouracil; ITT, intention to treat; N, nodular; PP, per protocol; S, superficial.

observed in 83% of the patients, but typically cleared up during the follow-up period. Forty-seven percent of the patients had ulcerations at the treatment site. The lowest incidence and severity of reactions occurred with 0.5 mL 5-FU–epinephrine gel three times weekly for 2 weeks.

### Comments

The analysis was per protocol. Concealment of allocation was unclear. No sample size calculation was described.

### Implications for clinical practice

High local drug concentrations can be maintained for longer with the epinephrine gel delivery of 5-FU. A trial of 5-FU–epinephrine gel versus surgical excision, monitoring adverse effects, is required to confirm the claim that the response rates are comparable to those with surgery.

### Imiquimod

Imiquimod is an immune-response modifier. It induces cytokines that promote a TH1 lymphocyte or cell-mediated immune response [60–62]. These cytokines include interferon alfa and gamma, and interleukin-12. In animal studies, imiquimod has demonstrated broad antiviral and antitumor effects that are largely mediated by interferon alfa [61]. In humans, imiquimod 5% cream is safe and effective in the treatment of external anogenital warts [63,64]. More recently, imiquimod has been licensed in the UK for superficial BCC. We found 10 RCTs, which are summarized in Table 33.7.

### Efficacy compared with vehicle cream

One study of 35 patients evaluated the safety and efficacy of imiquimod 5% cream in the treatment of superficial and nodular BCC [65,66]. This small trial suggested short-term success rates similar to those of excision surgery, with the added advantage of no scarring.

In a phase II dose–response trial of imiquimod 5% cream applied for 6 weeks in 99 Australian patients with primary superficial BCC [67], histological clearance rates (defined as patients with no histological evidence of BCC when the site of the treated lesion was excised 6 weeks after imiquimod treatment) were 100% (all of three), 88% (29 of 33), 73% (22 of 30), and 70% (23 of 33) for twice daily, once daily, six times weekly, and three times weekly regimens, respectively.

Another similar multicenter RCT of 128 patients with superficial BCC compared imiquimod twice daily, once daily, 5 days/week, and 3 days/week with vehicle using the same end points [68]. The intention-to-treat analysis showed clearance rates of 100% (10 of 10), 87% (27 of 31), 81% (21 of 26), and 52% for the twice daily, once daily, 5 days/week, and 3 days/week groups, respectively. Interestingly, there was a small vehicle response rate: 19% (six of 32).

Pooled data from two identical industry-funded studies [69] conducted in the USA in 724 patients with superficial BCC compared imiquimod daily either five times per week or seven times per week for 6 weeks versus vehicle. The histological clearance rates for the five times weekly and seven times weekly imiquimod groups were 82% and 79%, respectively.

One further industry-sponsored trial conducted in Europe [70] in 166 patients evaluated imiquimod 5% cream for the treatment of superficial BCC. At 12 weeks posttreatment, composite clearance was demonstrated in 77% (95% CI, 67–85%) and 6% (95% CI,

3–13%) of patients treated with imiquimod and vehicle cream, respectively ( $P < 0.001$ ), and histological clearance was demonstrated in 80% (95% CI, 70–87%) and 6% (95% CI, 3–13%), respectively ( $P < 0.001$ ).

Two similar studies [71] of 93 and 90 patients with superficial BCC and nodular BCC, respectively, found no significant difference in the treatment failure rate when occlusion was used.

Two further industry-sponsored trials [72] conducted in the USA have evaluated imiquimod 5% cream for the treatment of nodular BCC. One study reported histological clearance rates of 71% (25 of 35) for once-daily treatment for 6 weeks. Another vehicle-controlled RCT of 92 patients with nodular BCC who underwent treatment for 12 weeks using twice daily, once daily, 5 days/week, or 3 days/week reported intention-to-treat histological clearance rates of 75% (three of four), 76% (16 of 21), 70% (16 of 23), and 60% (12 of 20), respectively, with a vehicle response rate of 13% (three of 24).

One study [73] compared the tolerability of two regimens for the treatment of superficial BCC (Table 33.7). There was no significant difference in clearance rate at 19 weeks; however, there was a significant difference at 52 weeks (43% vs 88%) in favor of 5% imiquimod cream once daily with a 1 week interval. Both regimens were well tolerated.

One study [74] compared imiquimod three times a week over 8 weeks versus three times a week over 12 weeks in patients with nodular BCC. There were no significant differences between the treatment arms with respect to efficacy or tolerability. Clinical clearance was found in 70/90 patients. Histopathological clearance was seen in 58 patients. In 12 patients, despite complete clinical clearance, tumor was still detected in histopathological evaluation.

### Potential drawbacks

There may be some local skin reaction to the cream, including: redness, edema, skin hardening, vesicles, erosion, ulceration, flaking, and scabbing. These brisk inflammatory reactions, at least clinically, would be consistent with an acute immunologic reconstitution of the sun-damaged skin, resulting in an immunologically mediated elimination of malignant and premalignant cells. In all studies, local reactions were common, mostly mild or moderate, were well tolerated by patients, and declined in incidence and severity with less frequent dosing [65–67,69,71,72].

### Comment

There was no long-term follow-up for recurrence, which is very important for assessing treatments. Increasing severity of erythema, erosion, and scabbing/crusting was associated with higher clearance rates. Patients were able to apply the cream themselves in all of the trials – a feature that could reduce the need for attendance at busy hospital departments for low-risk lesions.

Clinical clearance does not accurately reflect the presence or absence of disease.

### Implications for clinical practice

Topical imiquimod could become a useful treatment for superficial and low-risk BCCs and would allow dermatologists to concentrate on the high-risk BCCs, but long-term results comparing topical imiquimod with excisional surgery are essential. A study of this type has just been completed and the protocol has been published [75]. The results for treatment success at 3 years (primary outcome) have been submitted for publication by the authors of this chapter.

**Table 33.7** Randomized controlled trials evaluating imiquimod 5% cream in the treatment of basal cell carcinoma

Study	Method	Participants	Interventions	Outcomes
Beutner <i>et al.</i> 1999 [65] (USA)	Single center Randomization to give 2:1 ratio of imiquimod cream to vehicle cream Method of randomization not known ITT	Age range 37–81 years BP BCCs, T1: 7; T2: 4; T3: 4; T5: 5; T6: 11 patients Size: 0.5–2.0 cm <sup>2</sup> Mainly upper body Histological type, T1: 1 N, 2 S; T2: 1 N, 3 S; T3: 4 S; T4: 2 N, 3 S; T5: 2 N, 2 S; T6: 1 N, 10 S	Imiquimod 5% cream, T1: twice/day; T2: once/day; T3: three times/week; T4: twice/week; T5: once/week; T6: vehicle	FU: 6 weeks after treatment. Tumor site excised and examined histologically
Marks <i>et al.</i> 2001 [67] (Australia, New Zealand)	Multicenter Method of randomization not known ITT	72 male, 27 female HP S BCC; surface area 0.5–2.0 cm <sup>2</sup> Location: 32% upper limbs, 28% trunk, 40% head and neck	Imiquimod 5% cream: T1: twice/day; T2: once/day; T3: twice/day for 3 days/week; T4: once/day for 2 days/week	FU: 1, 2, 4, 6 weeks Excision at week 6 Lost to FU, T2: 2 (pruritus); T3: 1 (cerebrovascular accident); T4: 1 (excision of nearby tumor)
Geisse <i>et al.</i> 2002 [68] (USA)	Multicenter, randomized, blinded, vehicle-controlled dose–response Method of randomization not known ITT	128 patients. Single, primary BP S BCC (0.5–2.0 cm <sup>2</sup> )	Imiquimod for 12 weeks, T1: twice daily; T2: once daily; T3: Mon–Fri; T4: Mon, Wed, Fri	FU: surgical excision 6 weeks after treatment
Sterry <i>et al.</i> 2002 [71] (Europe)	Multicenter, randomized open-label, dose–response Method of randomization not known ITT	Two studies. HP BCC. 93 N BCC (0.5–2.0 cm <sup>2</sup> ), 90 S BCC (0.25–1.5 cm <sup>2</sup> )	T1/T2: imiquimod 3 times/week for 6 weeks with (T1) and without (T2) occlusion; T3/T4: twice/week for 6 weeks, with (T3) and without (T4) occlusion	FU: surgical excision 6 weeks after treatment
Shumack <i>et al.</i> 2002 [72] (USA)	Two studies: multicenter, randomized, open-label, dose–response and a multicenter, randomized, blinded, vehicle-controlled dose–response Method of randomization not known ITT	Study 1: 99 patients, single, primary, BP N BCC (0.5–2.0 cm <sup>2</sup> ) Study 2: 92 patients, single, primary BP N BCC (0.5–2.0 cm <sup>2</sup> )	Study 1: imiquimod for 6 weeks, T1: twice daily; T2: once daily; T3: twice daily 3 days/week for 6 weeks; T4: 3/week for 6 weeks Study 2: imiquimod for 12 weeks, T1 twice daily; T2: once daily; T3: Mon–Fri; T4: Mon, Wed, Fri	FU: surgical excision 6 weeks after treatment
Schulze <i>et al.</i> 2005 [70] (Europe)	Multicenter, randomized, double blinded, vehicle-controlled Computer-generated randomization schedule ITT	166 patients, HP S BCC on limbs, trunk, neck, or head. Not high-risk areas. Minimum area 0.5 cm <sup>2</sup> and maximum diameter 2.0 cm	Imiquimod 5% cream or vehicle daily, 7×/week for 6 weeks	FU: excised 12 weeks posttreatment
Geisse <i>et al.</i> 2004 [69] (USA)	Multicenter, randomized, double-blinded, vehicle-controlled. Computer-generated randomization schedule ITT	724 patients with BP S BCC, (0.5 cm <sup>2</sup> in area with max. diameter of 2 cm)	Imiquimod 5% cream or vehicle, daily either 5×/week or 7×/week for 6 weeks	FU: weeks 4 and 12 posttreatment
Ezughah <i>et al.</i> 2008 [73] (UK)	Computer-generated randomization schedule	32 patients with S BCC (minimum area 0.5 cm <sup>2</sup> and maximum depth of 2 mm), T1: 15; T2: 16 patients	Imiquimod (two different regimens), T1: 8 weeks treatment with once daily dose for alternate weeks; T2: 5 weeks treatment, once daily dose with 1-week interval in the middle of course	FU: 19 and 52 weeks
Eigentler <i>et al.</i> 2007 [74] (Germany)		102 patients with N BCC randomized Evaluable (N = 90)	Imiquimod thrice-weekly for either 8 or 12 weeks	12 patients dropped out

BCC, basal cell carcinoma; BP, biopsy-proven; FU, follow-up; HP, histologically proven; ITT, intention to treat; N, nodular; S, superficial.

Imiquimod has also been explored as adjuvant therapy for patients undergoing other treatment, but these studies are not covered in this chapter.

### Systemic therapy for basal cell carcinoma

Vismodegib is a small-molecule systemic inhibitor of the hedgehog Hh intracellular signaling pathway that is inactive in adults. This pathway is active in BCCs and in patients with nevroid BCC syndrome. Vismodegib is licensed for treatment of metastatic and locally advanced recurrent tumors inappropriate for surgery or radiotherapy. In an open-label, two-cohort Phase 2 study of meta-

static BCC and locally advanced BCC, a 30.3% partial response rate was seen with no complete responses in metastatic BCC and a 43% response in locally advanced disease with 21% of these having complete response [77]. In an RCT of vismodegib versus placebo in the treatment of 41 patients with basal cell nevus syndrome [78], treatment was associated with a reduction from an average of 29 tumors per participant during the observation period of 8 months to two and the safety committee stopped the placebo arm of the trial. Many tumors cleared histologically during treatment; however, 54% withdrew due to side effects, particularly dysgeusia/ageusia, weight loss, muscle cramps, and hair loss. Stopping treatment was

associated with the return of the original tumors but a reduced new tumor burden developing in the period of observation so far. Adverse effects settled within 4 weeks of stopping therapy.

This is clearly an interesting development in the management of advanced BCC, but further work is needed to define the best clinical situations and dosage regimes for the use of this agent, especially in view of the troublesome side effects.

### Key points

- Despite the enormous amount of work involved in the treatment of BCC, there are still very few good-quality RCTs concerning the efficacy of the treatment modalities used.
- Surgery and radiotherapy appear to be the most effective treatments.
- The majority of studies have been performed on low-risk BCCs, the results of which are probably not applicable to tumors of the morpheic type shown in Figure 33.3.
- Cryotherapy, although convenient and less expensive than surgery or radiotherapy, has poor cure rates in comparison with surgery or radiotherapy (especially for lesions >2 cm). The cosmetic effect is better with surgery and comparable to radiotherapy.
- If cryosurgery is to be used, two freeze-thaw cycles are recommended for nodular and superficial facial lesions (Figures 33.1 and 33.2) if cure rates approaching equivalence to those with formal excision or radiotherapy are to be achieved.
- Greater efficacy needs to be demonstrated for PDT in nodular BCC and interferon before they can be recommended.
- A broadband halogen light source may give cure rates and cosmetic outcome similar to laser light PDT, with the possible benefits of reduced costs, increased safety, and ease of use, although both are inferior to surgery.
- The efficacy of interferon alfa has not been directly compared with standard surgical treatment; interferons are associated with significant side effects, which may overshadow their usefulness, especially in the elderly. Interferon therapy requires several clinic visits.
- Increased short-term eradication of BCC using 5-FU in a PC-based vehicle to increase penetration should be compared with surgery, with long-term follow-up.
- Preliminary studies suggest a high success rate (87–88%) for imiquimod in the treatment of superficial BCC using a once-daily regimen for 6 weeks, and a useful (76%) treatment response when treating nodular BCC for 12 weeks. A long-term study has just been completed with excision surgery as a comparator.
- All future RCTs of BCC treatment should include 3–5-year outcomes, as short-term (less than 1 year) improvement may simply be a temporary phenomenon. This is especially important for topical application, which may appear to improve the surface of the lesion only to leave deeper extensions that the dermatologist may find it difficult to see on clinical examination.

### Vismodegib in advanced basal-cell carcinoma

- Hedgehog antagonist GDC-0449 in the treatment of advanced basal cell carcinoma – initial studies have shown that GDC-0449 has shown significant inhibitory activity in the treatment of advanced BCC [76].

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# Primary cutaneous T-cell lymphoma

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## Background

### Definition

Primary cutaneous T-cell lymphomas (CTCLs) represent a heterogeneous group of extranodal non-Hodgkin's lymphomas, of which mycosis fungoides (MF) and Sézary syndrome (SS) are the most common clinicopathological subtypes [1]. MF is characterized by distinct clinical stages of cutaneous disease consisting of patches/plaques, tumors, and erythroderma in which the whole skin is involved. Peripheral adenopathy may or may not be present. SS is defined by the presence of erythroderma, peripheral lymphadenopathy, and a minimum number of Sézary cells within the peripheral blood. These clinicopathological entities are closely related pathogenetically, but are distinct from other less common types of primary CTCL.

### Incidence and prevalence

The overall annual incidence of primary CTCL is 7.7/1 000 000 person-years (MF or SS 4.1/1 000 000) with a male predominance [2]. However, the prevalence is much higher, because most patients have low-grade disease and live long [3]. Males and the black population are affected more commonly [2–4]. The incidence has increased during the past two decades, but this almost certainly partly reflects improved diagnosis of earlier stages and better registration, particularly in the USA [4].

### Etiology

The underlying etiology is unknown. There is evidence for inactivation of key tumor suppressor genes and TH2 cytokine production by tumor cells in MF/SS, but no disease-specific molecular abnormality has yet been identified [4]. Primary CTCL must be distinguished from human T-lymphotropic virus type-1 (HTLV-I)-associated adult T-cell leukemia lymphoma (ATLL), in which skin involvement often closely mimics the clinicopathological features of MF or SS and may be the presenting feature [1].

### Staging and prognosis

For MF/SS two staging systems are in regular use, including the TNMB (primary tumor, regional nodes, metastasis, blood) system,

revised in 2007 [5], and a clinical staging specifically designed for CTCL (Box 34.1) [6].

Most cases of primary CTCL are not curable. The majority of patients present with early-stage disease, and those with patches alone have a lower risk of progression than those with both patches and plaques. A recent multivariate analysis in a cohort of 1502 patients with MF or SS, using the revised TNMB classification, has identified risk factors for progression and survival and helps to define distinct risk groups, particularly for early-stage patients [7]. Male gender and age >60 are key risk factors. In early-stage disease, the presence of plaques, folliculotropic disease, and palpable or histologically confirmed dermatopathic lymph nodes are also poor prognostic factors [7]. The lymph-node status and tumor burden within peripheral blood determine the prognosis in SS [6,8]. Multivariate analysis indicates that an initial complete response (CR) to various therapies is an independent favorable prognostic feature, particularly in early stages of disease [9–12].

Table 34.1 summarizes actuarial survival data for MF [3,7,10–14]. Patients with early (stage IA) MF are unlikely to die of their disease; however, the prognosis of stage IB disease is more variable and partly determined by age, gender, the presence of folliculotropism, and the presence of an identical peripheral blood T-cell clone in the skin and blood.

Although the prognosis in stage IB patients is worse, there is a marked variation, and this probably reflects its heterogeneous nature, both in terms of tumor burden and biology [3,10].

The survival data for patients with erythrodermic MF but no evidence of lymph-node or peripheral blood involvement (stage III) are similar to those for stage IIB disease [3,11,14]. In contrast, the overall survival and disease-specific survival rates at 5 and 10 years for stages IVA and IVB patients is poor [7,10,13,14].

Other clinicopathological variants of CTCL are generally associated with an excellent long-term prognosis (100% 5-year survival in lymphomatoid papulosis and 90% in primary cutaneous CD30+ve anaplastic large-cell lymphoma (ALCL)), with the exception of patients with subcutaneous panniculitis-like T-cell lymphomas and primary cutaneous natural-killer (NK)-like T-cell lymphomas [1].

**Box 34.1** The recently revised TNMB (primary tumor, regional nodes, metastasis, blood) classification for MF/SS

### Skin

- T1, limited patches/plaques (<10% of total skin surface)
  - T1a – patches only; T1b – plaques ± patches
- T2, extensive patches/plaques (>10% of total skin surface)
  - T2a – patches only; T2b – plaques ± patches
- T3, tumors
- T4, erythroderma (confluent erythema >80% body surface area)

### Nodes

- N0, no clinical lymphadenopathy
- N1, clinically enlarged lymph nodes but histologically uninvolved (dermatopathic)
  - N1a – clone negative; N1b – clone positive
- N2, clinically abnormal lymph node, histologically NCI LN3
  - N2a – clone negative; N2b – clone positive
- N3, clinically abnormal lymph nodes and histologically NCI LN4, clone positive or negative
- Nx, clinically abnormal lymph nodes without histologic confirmation

### Visceral

- M0, no visceral involvement
- M1, visceral involvement (organ should be specified)

### Blood

- B0, no peripheral blood Sézary cells (<5%)
  - B0a – clone negative; B0b – clone positive
- B1, low blood tumour burden: >5% of total lymphocyte count Sézary cells but does not meet criteria of B2
- B2, high blood tumor burden:  $\geq 1000/\mu\text{l}$  Sézary cells with positive clone or  $\text{CD4/CD8} \geq 10$ ,  $\text{CD4+CD7}^-$  cells  $\geq 40\%$  or  $\text{CD4+CD26}^-$  cells  $\geq 30\%$

### Clinical staging system for MF or SS [6]

Stage	T	N	M	B
IA	T1	N0	M0	B0,1
IB	T2	N0	M0	B0,1
IIA	T1–2	N1,2, X	M0	B0,1
IIB	T3	N0–2, X	M0	B0,1
IIIA	T4	N0–2, X	M0	B0
IIIB	T4	N0–2, X	M0	B1
IVA1	T1–4	N0–2, X	M0	B2
IVA2	T1–4	N3	M0	B0–2
IVB	T1–4	N0–3, X	M1	B0–2

## Diagnostic tests

The diagnosis of different variants of primary CTCL is based on careful assessment of the clinical and histopathological features. Repeated biopsies may be required to establish the diagnosis, and clinicopathological correlation is essential. Immunophenotypic studies are required to identify different CTCL variants, and analysis of T-cell receptor genes in DNA extracted from skin biopsies can identify a T-cell clone, which helps to confirm the diagnosis. However, T-cell clones are not always detected in early stages of MF

because of a lack of sensitivity. Investigations – including a computed tomography (CT) scan of the chest, abdomen, and pelvis to exclude systemic involvement and assessment of peripheral blood for Sézary cells and lymphocyte subsets – are indicated in all patients, with the exception of those with early stages of MF (IA/IB) and lymphomatoid papulosis [15]. Bone-marrow aspirate/trephine biopsies are indicated in CTCL variants, but rarely in MF and SS.

## Aims of treatment

The aim of treatment is to induce complete or partial remission of disease and to prolong the disease-free survival and overall survival, while maintaining the patient's quality of life (Table 34.2).

## Clinical endpoints and response criteria

Historically, most trials in CTCL have been retrospective reports of case studies or phase II trials with no standardized definition of endpoints or response criteria. Most studies have reported responses based on skin disease alone, and assessments have been of variable quality with CR defined as complete resolution of clinically apparent disease for at least 4–6 weeks. Partial response (PR) is usually defined as >50% reduction of clinical disease or tumor burden, although some studies have defined this as >25% reduction in tumor burden. Stable disease (SD) is usually defined as <50% improvement, and progressive disease (PD) as >25% increase in tumor burden. For most studies PD has been defined as deterioration in the clinical stage of the disease. A quality-of-life assessment for CTCL has been published, although this has rarely been assessed in studies [16].

In 2011, the ISCL–EORTC published consensus criteria for disease endpoints and assessment tools for MF/SS, using a global scoring system, based on response in all tumor compartments. This should be used in all clinical trials, but also adopted for all patients to help accurately assess tumor burden and response to therapy [17].

- There should be accurate definitions of patches, plaques, and tumors.
- Histopathological diagnosis should be confirmed by a pathologist with expertise in cutaneous lymphoma.
- Assessment of skin involvement should be performed using the modified severity weighted assessment tool (mSWAT). This enables direct assessment of body surface area of each type of MF or SS lesion in each of the 12 areas of the body, multiplying the sum of the body surface area of each lesion by a weighting factor (patch  $\times 1$ , plaque  $\times 2$ , tumor  $\times 4$ ) [18,19].
- Assessment of lymph node and visceral involvement by staging CT scans and lymph node biopsy.
- Assessment of blood involvement with Sézary count and lymphocyte subsets.
- Establishment of molecular remission using T-cell receptor gene analysis of skin and peripheral blood.
- Quality-of-life assessment, including quality-of-life scores and assessment of itch.

## Methods of search

Systematic reviews, controlled clinical trials, and clinical trials were located by searching the Cochrane Library (1999–2012) and Medline (1985–2012). Because of a limited number of randomized clinical trials (RCTs) and the overall low incidence of CTCL, some small studies are included, and the limitations of such studies are discussed.

**Table 34.1** Published outcomes according to clinical stage in cutaneous T-cell lymphoma.

	IA	IB	IIA	IIB	III	IVA	IVB	Overall	Reference	No. of patients	Median follow-up (years)
<b>Overall survival (%)</b>											
5 years	99	86	49	65		40	0	80	Doorn <i>et al.</i> 2000 [10] <sup>a</sup>	309	5.2
	100	84		52	57				Zackheim <i>et al.</i> 1999 [3] <sup>b</sup>	489	4.7
	96	(78)		(40)	(40)				Kim <i>et al.</i> 1996 [11] <sup>c</sup>	122	9.8
		73	73 <sup>d</sup>						Kim <i>et al.</i> 1999 [12] <sup>d</sup>	176	8
					45	17			Kim <i>et al.</i> 1995 [14] <sup>e</sup>	106	10.5
						15	15		Coninck <i>et al.</i> 2001 [13] <sup>f</sup>	112	
	94	84	78	47	IIIA 47 IIIB 40	IVA1 37 IVA2 18	18		Agar <i>et al.</i> 2010 [7] <sup>g</sup>	1502	5.9
10 years	84	61	49	27		20	0	57	Doorn <i>et al.</i> 2000 [10]	309	5.2
	100	67		39	41				Zackheim <i>et al.</i> 1999 [3]	489	4.7
	88	(60)		(20)	(20)				Kim <i>et al.</i> 1996 [11]	122	9.8
		58	45 <sup>d</sup>						Kim <i>et al.</i> 1999 [12]	176	8
						5	5		Coninck <i>et al.</i> 2001 [13]	112	
	88	70	52	34	IIIA 37 IIIB 25	IVA1 18 IVA2 15	NR		Agar <i>et al.</i> 2010 [7]	1502	
<b>Disease-specific survival (%)</b>											
5 years	100	96	68	80		40	0	89	Doorn <i>et al.</i> 2000 [10]	309	5.2
	98	89	89	56	IIIA 54 IIIB 48	IVA1 41 IVA2 23	18		Agar <i>et al.</i> 2010 [7]	1502	5.9
10 years	97	83	68	42		20	0	75	Doorn <i>et al.</i> 2000 [10]	309	5.2
	98								Kim <i>et al.</i> 1996 [11]	122	9.8
	95	77	67	42	IIIA 45 IIIB 45	IVA1 20 IVA2 20	NR		Agar <i>et al.</i> 2010 [7]	1502	5.9
<b>Median survival (years)</b>											
	NR	12.1		2.9	3.6				Kim <i>et al.</i> 1996 [11]	556	9.8
		12.8	10.0						Kim <i>et al.</i> 1999 [12]	176	8
					4.6	1.1			Kim <i>et al.</i> 1995 [14]	106	10.5
						0.25	1.1		Coninck <i>et al.</i> 2001 [13]	546	
	35.5	21.5	15.8	4.7	IIIA 4.7 IIIB 3.4	IVA1 3.8 IVA2 2.1	1.4		Agar <i>et al.</i> 2010 [7]	1502	5.9
<b>Disease progression (%)</b>											
5 years	4	21	65	32		70	100		Doorn <i>et al.</i> 2000 [10]	309	5.2
	8	21	17	48	IIIA 53 IIIB 82	IVA1 62 IVA2 77	82		Agar <i>et al.</i> 2010 [7]	1502	5.9
10 years	10	39	65	60		70	100		Doorn <i>et al.</i> 2000 [10]	309	5.2
	12	38	33	58	IIIA 62 IIIB 73	IVA1 83 IVA2 80	NR		Agar <i>et al.</i> 2010 [7]	1502	5.9
20 years	0	10		36	41				Coninck <i>et al.</i> 2001 [13]	546	
	18	47	41	71	IIIA 74 IIIB NR	IVA1 86 IVA2 94	NR		Agar <i>et al.</i> 2010 [7]	1502	5.9



	IA	IB	IIA	IIB	III	IVA	IVB	Overall	Reference	No. of patients	Median follow-up (years)
Overall	9								Kim <i>et al.</i> 1996 [10]	122	9.8
		20	34 <sup>d</sup>						Kim <i>et al.</i> 1999 [12]	176	8
<b>Freedom from recurrence (%)</b>											
5 years	50								Kim <i>et al.</i> 1996 [11]	122	9.8
		36	9						Kim <i>et al.</i> 1999 [12]	176	8
10 years	25 (50)								Kim <i>et al.</i> 1996 [11]	122	9.8
		31	3						Kim <i>et al.</i> 1999 [12]	176	8

All overall survival (OS) curves were calculated using the Kaplan–Meier method.

<sup>a</sup>In the study by Doorn *et al.* [10], the presence of follicular mucinosis was an independent poor prognostic feature possibly related to depth of infiltrate in patients with stage IB disease (disease-free survival of 81% and 36% and OS of 75% and 21% at 5 years and 10 years, respectively). A lack of a CR to initial therapy was also associated with a poor outcome ( $P < 0.001$ ) in a multivariate analysis as well as increasing clinical stage and the presence of extracutaneous disease. A different staging system was used in this study but the staging has been altered to be consistent. Only three patients had stage IVB disease and only 18 patients each had stage IIA and IVA disease. Therefore, the results for these stages must be interpreted cautiously.

<sup>b</sup>In the study by Zackheim *et al.* [3], black patients had a relatively more advanced stage of disease than white patients. The TNM classification was used in this study. Lymph node stage had an unfavorable impact on survival but this trend did not reach significance for *each individual* T stage because of a lack of sufficient power (an estimated 1700 subjects required) and IIA/IVA patients were not designated separately. Similar considerations apply to peripheral blood involvement. Similar outcomes for patients with stage IIB (T3) and III (T4) disease are consistent with other studies, but this might reflect a lack of lymph node staging data included in this study.

<sup>c</sup>The 1996 study by Kim *et al.* [11] primarily included data on 122 patients with stage IA disease, but survival data on 556 patients with all stages were also included to give the values in parentheses. The free from relapse (FFR) data at 5 and 10 years are confusing because the text states that the FFR at 10 years was 25% but the figure indicates that it remains at approximately 50%, as for FFR at 5 years. The median survival for stage IA patients was not reached at 32.5 years. NR, not reached.

<sup>d</sup>In the 1999 study by Kim *et al.* [12], OS at 20 years for stage IB and IIA patients was 27%. DSS was better for patients <58 years of age ( $P < 0.03$ ). In 23 of the 56 patients with palpable lymphadenopathy, no histological assessment was made and these patients were assumed to have reactive/dermatopathic nodes (IIA). This might account for the lack of difference in OS at 5 years between stage IB and IIA patients, although there appears to be a difference in OS at 10 years.

<sup>e</sup>In the 1995 study by Kim *et al.* [14], the OS and median survival data were calculated from the date of initial treatment, which was usually within 3 months of diagnosis. This study also stratified patients into three groups according to the presence of none, one, or two or three poor prognostic parameters; namely: age at presentation (>65 years), the presence of clinical adenopathy, and B1 stage, producing varied median survivals of 10.2 years (no factors), 3.7 years (one factor), and 1.5 years (two or three factors);  $P < 0.005$ .

<sup>f</sup>The study by Coninck *et al.* [13] included 112 patients with extracutaneous disease at presentation or with progression and 434 patients with only cutaneous disease, giving the 546 patients listed in the table for median survival and disease progression.

<sup>g</sup>The study by Agar *et al.* [7] studied the largest cohort of patients and was the first to validate the recent International Society for Cutaneous Lymphomas (ISCL)–European Organisation for the Research and Treatment of Cancer (EORTC) staging proposal

**Table 34.2** Treatment of MF or SS.

Stage	First-line treatment	Second-line treatment	Experimental	Not suitable
IA	SDT or no therapy	SDT or no therapy	Bexarotene gel 5% imiquimod cream	Chemotherapy
IB	SDT	Interferon alpha + PUVA, bexarotene, TSEB, HDACi <sup>a</sup> (clinical trial)	Denileukin diftitox, antibody therapies	Chemotherapy
IIA	SDT (clinical trial)	Interferon alpha + PUVA, bexarotene, TSEB (clinical trial)	Denileukin diftitox, antibody therapies	Chemotherapy
IIB	Radiotherapy or TSEB therapy, chemotherapy (Clinical Trial)	Interferon alpha, denileukin diftitox, <sup>a</sup> bexarotene, HDACi (clinical trial)	AHSCT, antibody therapies	
III	PUVA ± interferon alpha, ECP ± interferon alpha, ± bexarotene methotrexate (clinical trial)	TSEB, denileukin diftitox, <sup>a</sup> HDACi, <sup>a</sup> chemotherapy, alemtuzumab (clinical trial)	AHSCT, antibody therapies	
IVA	Radiotherapy or TSEB therapy, chemotherapy (clinical trial)	Interferon alpha, denileukin diftitox, <sup>a</sup> alemtuzumab, bexarotene HDACi <sup>a</sup> (clinical trial)	AHSCT, antibody therapies	
IVB	Radiotherapy, chemotherapy (clinical trial)	Palliative therapy (clinical trial)	AHSCT	

HDACi, histone deacetylase inhibitor; ECP, extracorporeal photopheresis; AHSCT, allogeneic hematopoietic stem cell transplant; PUVA, psoralen + ultraviolet A; SDT, skin-directed therapy including topical emollients, steroids, mechlorethamine, carmustine, bexarotene gel, UVB/PUVA, superficial radiotherapy; TSEB, total skin electron beam. Antibody therapies – other than alemtuzumab.

Stage III includes Sézary syndrome, although some cases of Sézary syndrome will be stage IVA. ECP is ideal for patients with peripheral blood involvement.

<sup>a</sup>Not yet licensed in Europe.

## Questions

### What are the effects of topical therapy in mycosis fungoides?

#### Topical corticosteroids

##### Efficacy

No systematic reviews or RCTs were identified. One large open uncontrolled study of 79 patients with MF (stage T1/T2) who were treated with class I to III (potent/moderate potency) topical corticosteroids twice daily for 3–4 months and under occlusion showed CR in 63% and PR in 31% of stage T1 patients, and CR and PR in 25% and 57%, respectively, for patients with stage T2 [20]. CR was confirmed histologically in seven patients, but the median duration was not documented.

##### Drawbacks

Reversible depression of serum cortisol levels occurred in 13% of patients, and skin atrophy in one patient.

##### Comment

The lack of controlled studies and a short median follow up of 9 months weakens the impact of the results. No evidence of impact on disease-specific survival or overall survival was reported. However, topical corticosteroids, especially class 1 (potent) compounds, are effective at temporarily clearing patches and plaques in some patients with early-stage IA/IB MF.

#### Topical mechlorethamine (nitrogen mustard)

##### Efficacy

A randomized, controlled, observer-blinded, multicenter study involving 260 patients with stage IA–IIA disease evaluated the safety and efficacy of mechlorethamine 0.02% gel compared with ointment when used once daily for up to 12 months. Response rates were similar in both groups for the primary endpoint, composite index lesion severity assessment (58.5% versus 47.7%) and mSWAT analysis (46.9% versus 46.2%); however, time-to-response analysis showed superiority of the gel compared with the ointment formulation. Similar numbers of patients in the gel (20.3%) and ointment arms (17.3%) withdrew because of drug-related skin irritation [21].

A prospective nonrandomized study of 64 patients with early-stage MF treated with a 0.02% aqueous solution of mechlorethamine followed by betamethasone cream twice weekly for 6 months reported 58% CRs. Overall, 28% developed severe cutaneous intolerance, and relapse was observed in 46% after a mean of 7.7 months [22].

A retrospective, single-center review of 123 patients treated with whole-body once-daily application of topical mechlorethamine (10–20 mg/mL; aqueous preparation from 1968 to 1980 and ointment base from 1980 to 1985) until maximum response reported CRs of 51% in IA, 26% in IB, 0% in IIB, and 22% in stage III disease [23]. There were no differences in outcome with the aqueous or ointment base. Fifty patients had received total skin electron beam (TSEB) therapy before topical mechlorethamine; 56% of patients who achieved CR relapsed despite maintenance treatment for 1–2 years [23].

A study of 117 patients reported a CR of 76% with stage I, 45% with stage II, and 49% with stage III disease within 2 years of therapy (median response duration 45 months) [24]. Patients were allowed local radiotherapy for tumors and were not excluded as responders. The overall 5-year survival was 89%.

In a retrospective review, 331 patients (1968–1982) were treated with topical mechlorethamine daily and with maintenance therapy daily or alternate days for at least 3 years for those with a CR. A CR lasting 4–14 years was observed in 20%, but only in those with stage IA–IB [25]. However, patients were allowed other therapies, including radiotherapy, TSEB therapy, phototherapy, and methotrexate to achieve a response. Relapse occurred in only 17% of these patients within 8 years of therapy being withdrawn, suggesting that some patients with very early-stage disease may have achieved a cure. Response rates were highest in the early stages of disease (IA, 80%; IB, 68%; IIA, 61%; IIB, 49%; III, 60%; IVA, 13%; IVB, 11%). The stage-specific 5/10-year survival rates were 94/89% (IA), 85/83% (IB), 82/67% (IIA), 59/31% (IIB), 75/49% (III), 20/13% (IVA), and 11/0% (IVB) [24]. In a prospective open study, 64 patients with stage IA–IIA MF were treated with twice-weekly mechlorethamine (0.02% aqueous solution) to the whole skin surface (with the exception of the head), followed by immediate topical application of betamethasone cream for 6 months [26]. Overall, 58% achieved a CR after a mean treatment duration of  $3.6 \pm 2.5$  months (20 of 33, 61%, with stage IA; 15 of 26, 58%, with stage IB; and two of five, 40%, with stage IIA). Eighteen patients (28%) developed severe cutaneous reactions necessitating treatment withdrawal, and the CR rates were significantly lower in these patients. Relapse occurred in 17 patients (46%) after a mean duration of  $7.7 \pm 6.5$  months from CR.

A retrospective study of 203 stage I–III patients treated with topical mechlorethamine (10–20 mg/100 mL) to the whole skin surface once daily until CR, as the initial therapy, revealed an overall response (OR) rate of 83% and a CR of 50%, with a median time to response of 12 months and median time to relapse of 12 months despite maintenance therapy [27]. Responses were better for early-stage IA disease (65% CR) than for stage IB (34% CR). Only 10% of patients developed contact reactions with the ointment preparation, and only 8% developed secondary malignancies. Pediatric patients ( $n = 6$ ) were also treated, with no significant toxicity. Overall, 68% of the patients were only treated throughout the follow-up period with topical mechlorethamine, and in this group the ORs were higher (T1, 77% CR; T2, 53% CR), with relapse-free rates of 74% and 54% for T1 and 54% and 29% for T2 at 2 and 5 years, respectively.

##### Drawbacks

An irritant contact dermatitis occurs in up to 40% of patients. This is less common with the ointment (0.01–0.02%). It is carcinogenic, and secondary cutaneous malignancies have been attributed to its long-term use (8.6-fold and 1.8-fold increased risk for squamous cell carcinoma and basal cell carcinoma, respectively). Home use is acceptable, with patients applying topical treatment overnight; however, partners should avoid contact, especially if pregnant. Appropriate protection for staff members applying topical therapy in the hospital setting is required, although no toxic effects have been reported [28].

##### Comments

Mechlorethamine is an effective topical therapy for early-stage (patches/thin plaques) MF. However, most studies are retrospective and confounded by the use of other therapeutic modalities. Duration of response varies, and the efficacy of maintenance therapy and whole-body application remains unclear, but some patients with stage IA disease may appear to be cured. The survival data reported for topical mechlorethamine are similar to those for

patients with early-stage disease (Table 34.1). Almost all patients with stage IA MF have a normal life expectancy, and so controlled trials are required.

### Topical carmustine

#### Efficacy

No RCTs were identified. A retrospective review of therapy in 143 patients revealed CRs in 86% of stage IA, 47% of stage IB, 55% of stage IIA, 17% of stage IIB, 21% of stage III, and 0% of stage IV patients [29]. Median time to CR was 11.5 weeks. Alternate day or daily treatment with 10 mg 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in dilute (95%) alcohol (60 mL) or 20–40% BCNU ointment can be used.

#### Drawbacks

Contact hypersensitivity is uncommon (10%), but bone-marrow suppression is common (30%). Total doses should not exceed 600 mg per course, and repeated courses may be required. Maintenance therapy should be avoided. The ointment is more stable than the alcohol solution.

#### Comments

Limited data suggest similar efficacy to mechlorethamine, but it is more extensively absorbed and therefore has a significant risk of bone-marrow suppression. It may help in patients with early-stage disease that show an irritant or allergic contact reaction to mechlorethamine. Comparative trials are needed.

### Topical retinoids

#### Efficacy

No RCTs were found. A prospective phase I/II open study of 0.1–1% bexarotene gel as incremental doses in 67 patients with stage IA/IB/IIA disease (initially alternate-day treatment, increasing to a maximum of four times daily if tolerated) showed a response rate of 63%, with 21% of patients showing a CR [30]. The median time to response and the duration of the response were 20 weeks and 99 weeks, respectively.

#### Drawbacks

Mild/moderate pruritus, burning pain, and rash (12% irritant contact dermatitis) were common.

#### Comment

The lack of a placebo control makes interpretation difficult. It is not licensed in Europe but has been approved by the United States Food and Drug Administration (FDA) as 1% Targretin gel for the treatment of patients with stage IA/IB disease. Further controlled studies are required.

### Topical peldesine (BCX-34)

Peldesine is an inhibitor of purine nucleoside phosphorylase, an enzyme involved in purine degradation within lymphocytes.

#### Efficacy

One RCT has compared topical application of peldesine twice daily to the entire skin surface for 24 weeks with a placebo (vehicle control) in 90 patients with stage IA/IB MF [31]. A PR or CR occurred in 28% of patients treated with peldesine and 24% of patients treated with placebo ( $P = 0.677$ ).

### Drawbacks

A minority of patients noted minor pruritus and rash.

#### Comment

Although no significant efficacy is apparent, the results indicate a high placebo therapeutic response (mostly PR), which should be considered when interpreting the efficacy of different topical therapies in early-stage MF. Data on endpoints and freedom from relapse are lacking.

### Other topical therapies

#### Efficacy

A pilot study of four patients comparing imiquimod 5% cream with placebo for 16 weeks showed no clearance (defined as clearance of at least 90% of lesion) and no improvement (improvement of at least 50% of lesion size or surface change) with either imiquimod or placebo. The only adverse effect was mild lesional irritation [32]. An open-label, pilot study of six patients with stage IA–IIB disease showed complete histological clearance of index lesions in three of six patients treated with imiquimod 5% cream three times per week for 12 weeks. Clinical response was observed in two of four lesions treated in a fourth patient [33]. A study of eight patients (four MF, one ALCL) demonstrated CR of lesions in two of four MF patients (both stage IA) and in the patient with ALCL [34]. A further report suggests a CR to 5% imiquimod cream in comparison with placebo in one patient with stage IA disease after daily application to specific lesions for 4 months; response was assessed clinically and with posttreatment biopsies [35].

There is one report of six patients with early-stage CTCL that were treated with topical 5-fluorouracil cream for between 3 and 18 months. All responded (4/6 CR, 2/6 PR), suggesting that it may have efficacy in early stages of MF [36]. Tolerance to treatment was good, with only mild skin irritation.

Topical photodynamic therapy with 5-aminolevulinic acid (5-ALA) and 100 J/cm<sup>2</sup> red light has been reported to be effective in isolated cases and small case series for patches and plaques, with clinical and/or histological clearance in 50–100% of cases [37,38]. A phase II placebo controlled study using the photodynamic agent Hypericin in combination with visible light in patients with stable patch or plaque-stage disease resulted in a significant improvement in the majority of patients with CTCL after 6 weeks of twice-weekly therapy, whereas the placebo arm showed no response ( $P \leq 0.028$ ) [39].

The excimer laser, which emits monochromatic light in the UV range at a wavelength of 308 nm, has also shown CR of individual lesions in patients with stage IA disease in small case series [40,41].

#### Drawbacks

These topical therapies can only be used for limited areas, which is a significant limitation for patients with widespread cutaneous disease.

#### Comments

Apart from two small placebo-controlled studies [32,39], the other studies are based on limited case reports. There needs to be comparative studies with other topical therapies and radiotherapy to justify their use in CTCL. Until there are technical developments of these topical therapies to permit application to large areas, it is unlikely that they will become a standard form of skin-directed therapy for CTCL.

## What are the effects of phototherapy in mycosis fungoides and Sézary syndrome?

### Efficacy

No RCTs were found. Broadband ultraviolet B (UVB, 290–320 nm) phototherapy with maintenance therapy produced a CR in 83% of 35 patients with early-stage disease (IA/IB), with a median response time of 5 months and a median response duration of 22 months [42].

Narrowband UVB (TL-01; 311–313 nm) also produced a CR in six of eight patients with stage IA disease, with a mean duration of response of 20 months [43].

A retrospective study of 24 patients with stage IA/IB disease and patches only showed CRs in 13 (54%) and PRs in seven (29%), with a histological response confirmed in nine of 10 patients and a mean time to relapse of 12.5 weeks [44].

A retrospective study of 114 patients (19 treated with narrowband UVB, 95 with psoralen+UVA (PUVA)) showed that narrowband UVB was as effective as PUVA (CR 63% compared with 62% for PUVA) for early-stage MF, with no difference in time to relapse [45].

High-dose ultraviolet A1 (UVA1) phototherapy (340–400 nm; 100 J/cm<sup>2</sup>) on a 5-day per week basis was used in 13 patients until maximal response. Eleven patients showed a CR (mean number of sessions 22; cumulative dose 2149 J/cm<sup>2</sup>) and seven remained in CR after a mean follow-up period of 7.2 months [46].

### Drawbacks

UV-induced erythema/pruritus may occur. High cumulative doses of UVA contribute to an increased risk of nonmelanoma skin cancer.

### Comments

UVB phototherapy is an effective short-term therapy for patches and thin plaques, but the duration of disease-free remission varies and the treatment probably does not affect long-term survival rates. UVA1 penetrates more deeply than UVB and PUVA, but the clinical relevance has not yet been established. No adequate comparative studies between different forms of phototherapy and PUVA have been published.

## Psoralen+ultraviolet A photochemotherapy

### Efficacy

No RCTs were found. An open study of 82 patients treated with PUVA and followed for up to 15 years reported an overall CR of 65% (79% IA, 59% IB, 83% IIA) and mean cumulative doses of 134 J/cm<sup>2</sup> (IA), 140 J/cm<sup>2</sup> (IB), and 240 J/cm<sup>2</sup> (IIA), with a median time to CR of 3 months [47]; 67% of stage IA, 41% of stage IB, and 67% of stage IIA patients were free of disease at 2 years, but maintenance PUVA was given to most patients [46]. Survival rates at 5 and 10 years were 89% for stage IA, 78% for stage IB, and – surprisingly – 100% for stage IIA.

An open study of PUVA in 82 patients with CTCL showed a CR in 62% of patients, with an 88% CR in stage IA (mean cumulative dose 160 J/cm<sup>2</sup>), 52% in stage IB (498 J/cm<sup>2</sup>), and 46% in stage III disease (178 J/cm<sup>2</sup>). No responses were seen in stage IIB patients. The maximum duration of response was 68 months; 38% of the complete responders relapsed despite maintenance PUVA [48].

A further open study has shown that 56% of stage IA and 39% of stage IB patients with a CR had no recurrence of CTCL during a maximum period of 44 months' follow-up, despite no maintenance

therapy [49]. Data from a prospective cohort study suggests that maintenance therapy does not prevent future relapse in MF. A history of previous relapse was most strongly associated with future relapse [50].

A retrospective study of the long-term outcome following CR from PUVA monotherapy at a single institution, in 66 patients with stage IA and IB/IIA disease, reported that 50% of patients ( $n = 33$ ) maintained a CR after a median follow-up of 84 months, while 50% experienced a relapse, with a median disease-free interval of 39 months [51]. Maintenance PUVA was given to almost all patients with a CR/PR. The only significant difference between the two groups was a higher cumulative UVA dose and the number of PUVA sessions in those achieving a CR. There was no significant difference in the overall survival rate for the nonrelapse and relapse cohorts.

### Drawbacks

Adverse effects include nausea, phototoxic reactions, and skin carcinogenesis. The risk of nonmelanoma skin cancer is related to the cumulative dose and total number of sessions.

### Comments

Despite the lack of controlled trials, PUVA remains one of the most useful skin-directed therapies for early stages of MF. RCTs comparing PUVA with TL-01 and topical mechlorethamine would be helpful in early-stage disease (IA/IB). The role of maintenance therapy is unclear, but high cumulative doses entail a significant risk of squamous cell carcinoma. There appears to be little difference in disease-free survival and overall survival rates in patients treated with topical chemotherapy, phototherapy, and TSEB therapy, but it is difficult to compare without RCTs.

## Combination regimens involving photochemotherapy

### Efficacy

An RCT compared PUVA two to five times per week, plus interferon alpha, 9 MU three times per week, with interferon alpha plus acitretin, 25–50 mg/day, in 98 patients (maximum duration of treatment 48 weeks) [52]. In 82 patients with stage I/II disease, CR rates were 70% in the PUVA/interferon group in comparison with 38% in the interferon and acitretin group ( $P < 0.05$ ). Responses were assessed by clinical observation only. Time to response was 18.6 weeks in the PUVA/interferon group, compared with 21.8 weeks in the interferon and acitretin group ( $P = 0.026$ ). No data on response duration were reported. The total cumulative doses of interferon alpha were similar in both groups.

An open study of 69 patients compared PUVA and acitretin with PUVA alone in MF [52]. The cumulative dose of PUVA needed to achieve a CR was lower in the combined-treatment group, although the overall CR was similar in the two groups (73% and 72%, respectively). No data on response duration were documented [53].

Phase I and II studies of PUVA (three times weekly) combined with variable doses of interferon alpha (maximum tolerated dose of 12 MU/m<sup>2</sup> three times per week) in 39 patients with MF and SS reported an OR of 90%, (62% CR, 28% PR); 79% of stage IB, 80% of IIA, 33% of stage IIB, 63% of stage III patients, and 40% of stage IVA patients obtained a CR [54]. PUVA was continued as a maintenance therapy indefinitely, while interferon alpha was continued for 2 years, until disease progression or withdrawal due to adverse effects. The median response duration was 28 months and median survival 62 months [54].



A prospective phase II study of PUVA (three times weekly with maintenance PUVA after CR) combined with interferon alpha (escalating dose schedule of 3–12 MU three times weekly according to tolerability) in 63 patients with all stages (37 stage IB, 12 stage III) for 1 year reported a CR of 75%, with a median response duration of 32 months [55]. The overall 5-year disease-free survival rate was 75%. A second prospective phase II study assessing the combination of interferon alpha (6–18 MU/week) and PUVA in 89 patients with stage IA–IIA MF treated for 14 months showed an 84% CR, with sustained remission in 20% [56].

A phase III multicenter randomized trial of PUVA versus PUVA plus bexarotene in 93 patients (87 started treatment, 41 PUVA, 46 PUVA plus bexarotene) showed similar ORs of 71% in the PUVA arm and 77% in the combination arm. There was no significant difference in response duration; however, there was a trend towards fewer PUVA sessions and lower UVA dose required to achieve CR in the combination arm [57].

In another study of 14 patients with relapsed or refractory MF who received a combination of bexarotene plus PUVA three times per week there was an OR of 67% in the nine patients that completed the treatment course; five withdrew because of hyperlipidemia [58].

### Drawbacks

These were, as for PUVA, interferon alpha, bexarotene, and acitretin alone. In the RCT comparing PUVA and interferon alpha with acitretin and interferon alpha [52], similar rates of mild/moderate adverse effects were noted in both groups, but more patients discontinued treatment in the interferon/acitretin group because of adverse effects.

### Comments

The RCT comparing PUVA and interferon alpha with interferon alpha and acitretin shows that PUVA and interferon alpha is more effective than interferon alpha and acitretin in early-stage I/II disease. Weaknesses of this study include the lack of a validated scoring system to assess tumor burden and a lack of evidence that outcome was assessed blind to allocation status. The trial comparing PUVA alone with PUVA plus acitretin [53] suggests a reduction in the mean cumulative dose of PUVA to CR, but there is no evidence for increased overall efficacy in the retinoid–PUVA group. The combination of interferon alpha and PUVA appears to be highly effective in all stages of CTCL. It should be noted, however, that the overall remission rate may be similar to that with PUVA alone, and randomized data for duration of remission and cumulative UVA dose are urgently required.

The RCT comparing PUVA with PUVA plus bexarotene used a validated scoring system to assess tumor burden; however, only 93 of the 145 required patients were randomized owing to low accrual and, therefore, the study lacks power [57].

## What are the effects of immunotherapy in mycosis fungoides/Sézary syndrome?

### Interferon alpha

#### Efficacy

No RCTs have been reported, except as combination therapy (see above).

Table 34.3 summarizes the studies of interferon alpha in the treatment of MF/SS.

A small retrospective study of 17 patients with stage IA–IV MF comparing pegylated interferon alpha-2b plus PUVA with standard

**Table 34.3** Comparison of studies of interferon alpha in CTCL.

Study design	No. of patients	Stage of disease	Interferon alpha dose	Overall response (%)	CR (%)	Median response duration (months)	Disease-free survival rate (%)	Comments
RCT PUVA plus IFN versus IFN plus acitretin [52]	98	I–IV (82 stage I/II)	9 MU 3×/week (plus either PUVA 2–5×/week or acitretin 25–50 mg/day) for maximum 48 weeks		IFN/PUVA 70 IFN/acitretin 38 (in 82 patients with Stage I/II disease ( $P < 0.05$ ))	Not reported	—	Time to response between the 2 groups not significant (18.6 versus 21.8 weeks) Total cumulative doses of IFN similar in both groups
Open [59]	20	IB–III	50 MU/m <sup>2</sup> 3×/week for 3 months	45%		5	—	All heavily pretreated
Nonrandomized [60]	22	IA–IVA	Escalating schedule to 36 MU/day versus 3 MU/day for 10 weeks	64% (78 versus 37)	27	—	—	Objective response greater in those treated with dose-escalating schedule, but numbers too small for statistical comparison
Open [61]	43	I–IV	3–18 MU daily (escalating dose)	74% Stage I/II 88 Stage III/IV 63	26	—	21 (at 55 months)	Responses more common if no prior treatment
Phase II [62]	24	IVA/B	High dose (mean 65.5 MU/m <sup>2</sup> per week) on days 1–5 every 3 weeks	29%	4% (1 of 24)	—	—	Dose reductions necessary. No improved response on dose escalation
Open [63]	45	All stages (13 of 45 SS)	6–9 MU daily for 12 months. Acitretin 0.5 mg/kg per day added after 3 months if no response	62% after 12 months (including 11 patients on combined therapy)	—	—	—	Not possible to exclude possibility that response in interferon alpha nonresponder group due to delayed efficacy from continued interferon alpha

IFN, interferon alpha; PUVA, psoralen+ultraviolet A; RCT, randomized controlled trial; SS, Sézary syndrome.

interferon alpha-2b plus PUVA showed a higher overall response rate with less constitutional side effects in the pegylated interferon alpha-2b group. However, there was a higher rate of myelosuppression and liver toxicity [64].

### Drawbacks

The dose-limiting toxicity includes reversible hematological abnormalities, hepatitis, weight loss, headache, depression, and flu-like symptoms consisting of fever, myalgia, lethargy, and anorexia.

### Comments

The clinical efficacy in all stages of CTCL is supported by the CRs seen in uncontrolled studies. It appears that higher doses are more effective, but dose-limiting toxicity is a problem. Larger studies are required to confirm whether pegylated interferon alpha is appropriate in MF. Questions remain about the effect on disease-free survival and overall survival and the role of combined therapy with PUVA.

## Extracorporeal photopheresis

### Efficacy

No RCTs were reported. Response rates to extracorporeal photopheresis (ECP) vary widely between different study groups. A recent systematic review of ECP treatment in over 650 patients from 30 published studies showed a mean response rate of 63% (range 43–100%) [65]. Responses were assessed mostly using a scoring system similar to that devised for the original study [66] and were higher in those with erythrodermic CTCL [66–69]. CRs were recorded in 27 studies involving 527 patients with a mean CR of 20% [65]. The differences in response rates between centers may relate to different patient selection for treatment with ECP, such as the presence of a peripheral T-cell clone, stage of disease, prior treatment, ECP protocol, duration of ECP, and definition of response. Survival data have been reported in erythrodermic disease, with median survivals of 39–100 months from diagnosis [68–71].

There have been numerous small case series reported of stage III patients treated with combinations of ECP, interferon alpha and/or retinoids, including bexarotene, which suggest that combination therapy can be highly effective as both clinical and molecular remissions have been documented [65,70,72–79].

A randomized crossover study comparing ECP with PUVA in patients with nonerythrodermic (stage IB–IIA) MF has shown no clinical efficacy for ECP in early stages of the disease in comparison with PUVA [80].

In contrast, a multicenter, prospective study of 19 patients all with early-stage MF (three stage IA, 14 stage IB, and two stage IIA) showed an OR of 42% (seven PR, one CR), with a median of 12 ECP sessions (range, 3–32) given over a median of 12 months (3–32 months) and with an overall response duration of 6.5 months (range 1–48 months). Quality-of-life questionnaires also showed an improvement in emotional scores [81].

### Drawbacks

ECP is well tolerated. Mild lymphopenia and anemia can occur with long-term therapy. High cost and lack of availability mean that ECP will remain confined to specialist centers.

### Comments

Controlled trials are required to compare ECP with standard single-agent chemotherapy regimens in erythrodermic disease and spe-

cifically in SS. Some previous studies have not clearly defined their diagnostic criteria for erythrodermic CTCL, and others have included patients with nonerythrodermic disease. Combination therapy with ECP and interferon alpha is frequently used, but existing studies do not exclude a beneficial response to interferon alpha alone.

Studies suggest that ECP requires a minimum tumor burden within peripheral blood [82], and the only RCT of ECP in nonerythrodermic, early-stage disease suggests that it is not effective [80].

## What are the effects of systemic retinoids in mycosis fungoides and Sézary syndrome?

### Etretinate, acitretin, and isotretinoin

#### Efficacy

A systematic review (1988–1994) of open studies of oral retinoids in CTCL (MF and SS) showed a mean OR of 58% and a CR of 19%, with a median duration of response of 3–13 months [83].

A nonrandomized study of 68 patients with various stages of MF/SS compared isotretinoin with etretinate and found similar efficacy and toxicity (isotretinoin: CR 21%, PR 38%; etretinate: CR 21%, PR 46%) [84]. A phase II study of isotretinoin in 25 patients with MF (IB–III) showed an OR of 44%, with three patients achieving a CR, and a median response duration of 8 months using high doses (2 mg/kg per day) [85].

An RCT comparing PUVA and interferon alpha with PUVA and acitretin showed a significantly better response rate for PUVA and interferon alpha [52] (see above).

### Drawbacks

Adverse events include mucocutaneous erosions and xerosis, hyperlipidemia, hepatotoxicity, and teratogenicity.

### Comments

Acitretin and etretinate have some efficacy in the early stages of disease, but are no better and probably less effective than PUVA and interferon alpha.

## Bexarotene

### Efficacy

No RCTs were found. A phase II open trial compared two doses (6.5 mg/m<sup>2</sup> per day and 650 mg/m<sup>2</sup> per day) of oral bexarotene in 58 patients with refractory stage IA–IIA CTCL [86]. The optimal dose was 300 mg/m<sup>2</sup> per day in terms of response and tolerability. ORs of 20%, 54%, and 67% were noted at the 6.5 mg/m<sup>2</sup> per day, 300 mg/m<sup>2</sup> per day, and 650 mg/m<sup>2</sup> per day doses, respectively. Rates of disease progression were 47%, 21%, and 13%, respectively. Median duration of response at the highest dose level was 516 days. In late stages of disease (stage IIB–IVB), ORs of 45% (at 300 mg/m<sup>2</sup> per day) and 55% (at doses >300 mg/m<sup>2</sup> per day) were reported, with a relapse rate of 36% and a projected median duration of response of 299 days [87].

Another study reported a PR of only 14% after 8 weeks (increased to 22% when interferon alpha was added for a further 8 weeks) [88]. However, the median time to response with bexarotene monotherapy is 180 days, suggesting that a longer initial period on bexarotene alone would have achieved a greater response rate [88].

A retrospective review of 66 patients (19, stage IB–IIA; 47, stage IIB–IVB) treated with bexarotene, either alone or with one or more additional adjuvant therapies, showed that, of the 52 patients that completed over 1 month of therapy, 9% had a CR, 35% PR, 23%

SD, and 12% PD. The median time to maximal response was 3 months and the median response duration was 8 months. Responses were seen in 26% of early disease and 51% of advanced disease. The weakness of this study was that PRs were not graded and included if there was any improvement in skin, blood, or lymph node disease [89].

### **Drawbacks**

Reversible adverse effects included hyperlipidemia, central hypothyroidism, leukopenia, headache, and asthenia, as well as other retinoid adverse effects.

### **Comments**

These studies suggest a therapeutic efficacy for bexarotene in all stages of CTCL, but comparisons with other therapies and data on effects on disease-free survival and overall survival in later stages of disease are required. Combination with other therapies, including phototherapy and interferon alpha, appears to be well tolerated [56,90,91]. Although the combination of PUVA and bexarotene shows a similar OR to PUVA alone, there is a trend towards fewer PUVA sessions and a lower UVA dose in order to obtain a CR [57].

## **What are the effects of antibody and toxin therapies in mycosis fungoides and Sézary syndrome?**

### **Anti-CD4 monoclonal antibodies**

#### **Efficacy**

In a phase I/II trial, seven patients with MF were treated with a chimeric (murine/human) anti-CD4 monoclonal antibody with successive increasing doses (10, 20, 40 and 80 mg) twice weekly for 3 weeks. All patients showed short-lived clinical responses (one CR, two PR) with a median duration of 2 weeks [92].

A subsequent study from the same group showed a PR in seven of eight patients given higher doses (50–200 mg), with a median freedom from progression of 28 weeks [93].

### **Drawbacks**

Treatment was well tolerated, with no acute toxicity. There is a marked but temporary suppression of T-cell proliferative responses to phytohemagglutinin. There is no documented depletion of CD4 counts. The immunogenicity of the antibody is unclear.

### **Zanolimumab**

Zanolimumab is a fully human anti-CD4 monoclonal antibody specific for the CD4 receptor expressed on T-lymphocytes. In two phase II prospective, multicenter, open-label, uncontrolled studies in refractory CD4+ve CTCL (38 MF, nine SS), 17 weekly infusions were given at two treatment doses (280 mg/560 mg in early-stage disease, 280 mg/980 mg in advanced disease). An OR of 56% was obtained in the high-dose groups (15% in the 280 mg group) with a median response duration of 81 weeks. The main adverse effect was dermatitis [94].

### **Comments**

A further pivotal study is underway in the USA.

### **Alemtuzumab (Campath-1H)**

#### **Efficacy**

There are no RCTs. Phase II trials of alemtuzumab (a humanized anti-CD52 monoclonal antibody) in small cohorts of patients with advanced MF or SS have shown encouraging overall response rates

[95–103]. Over 100 patients have been treated in 10 reported studies. ORs have ranged from 37 to 100% and are typically short-lived. Responses are best in erythrodermic disease, where symptomatic benefit is often dramatic. In the majority of the studies alemtuzumab has been administered intravenously at the standard dose of 30 mg three times per week.

Table 34.4 summarizes the findings in six trials.

### **Drawbacks**

Severe neutropenia and opportunistic infections are common, including cytomegalovirus reactivation. There have been reports of possible cardiac toxicity [98], but in most reports the safety profile has been acceptable, even in elderly patients [102].

### **Comments**

Alemtuzumab is a humanized anti-CD52 antibody that binds to all lymphocytes. Prolonged responses can be achieved in erythrodermic MF and SS. Reduced-dose schedules have been shown to induce a response with avoidance of life-threatening infections and a reduction in hematological toxicity.

## **Denileukin diftitox (diphtheria interleukin-2 fusion toxin) Efficacy**

Denileukin diftitox (DD) is a fusion protein in which the receptor binding domain of the diphtheria toxin has been exchanged for that of the interleukin-2 (IL-2) molecule. The diphtheria-toxin-mediated activity will predominantly only affect cells that express the IL-2 receptor. It is given intravenously on five consecutive days repeated every 21 days for up to eight cycles.

A phase III placebo-controlled trial of 144 patients (less than three prior treatments) gave an OR of 44% (10% CR, 34% PR) compared with 15.9% for the placebo group. The OR was higher in the 18 µg/kg per day group compared with the 9 µg/kg per day group (49.1% versus 37.8%). There was also a significant prolongation of progression-free survival (PFS) compared with placebo [104]. There was a significant improvement in quality of life ( $P = 0.041$ ) and pruritus severity ( $P = 0.05$ ) in responders compared with non-responders at the study endpoint. In a phase III study evaluating the safety and efficacy of DD in 20 patients who relapsed after responding to DD in the previous trial, there was an OR of 40% with a median duration of response of 274 days [105].

A phase III open uncontrolled study of DD in 71 patients with stage IB–IVA CTCL and biopsies showing >20% CD25+ve (IL-2R) lymphocytes, showed an OR of 30% (10% CR) [106]. The median duration of response was 6.9 months. No difference in response rates or duration of response was noted between 9 and 18 µg/kg per day. The development of anti-DD antibodies did not affect response rates.

An open-label study of 36 patients with low CD25 expression (<20% CD25+ve cells on skin biopsy) showed a similar OR of 30.6% (33.3% early stage, 26.7% stage IIB or greater) with a median PFS of >487 days [107].

A phase I study of combined DD (18 µg/kg per day for 3 days out of 21 days) and escalating doses of bexarotene (75–300 mg/day) in 14 patients with relapsed or refractory CTCL showed an OR of 67% (four CR, four PR) and no increased toxicity [108].

### **Drawbacks**

Adverse effects include flu-like symptoms, acute infusion-related hypersensitivity effects, a vascular leak syndrome, and transient elevations of hepatic enzymes.

**Table 34.4** Comparison of studies of alemtuzumab in CTCL.

Study design	No. of patients	Stage of disease	Alemtuzumab dose	Overall response (%)	CR (%)	Median response duration (months)	Median overall survival (months)	Comments
Open [103]	19	III–IV	Increasing doses to 30 mg intravenous 3×/week for 4 weeks followed by subcutaneous administration for 8 weeks	84	47	6	41	Heavily pretreated patients
Phase II [95]	8		30 mg intravenous 3×/week for maximum of 12 weeks	50	25	NR		High rates of infectious complications
Phase II [96]	8	Advanced/refractory	30 mg intravenous 3×/week for maximum of 12 weeks	38	0	3		Significant hematological and immunosuppressive toxicity
Phase II [97]	22	III–IV	30 mg intravenous 3×/week for maximum of 12 weeks	55	32	12		
Phase II [100]	4 with MF		Reduced dose – maximum 10 mg 3×/week for maximum 3 weeks	75	0			Hematological toxicity reduced with lower dose
Prospective [101]	14	SS (11 relapsed refractory, 3 treatment naive)	10–15 mg 3×/week	85.7	21.4	12	35	Infectious complications in 28.6% (all had 15 mg dose)

MF, mycosis fungoides; SS, Sézary syndrome; NR, not recorded.

### Comments

DD is currently not licensed for use in Europe. Recent studies have demonstrated that it is possible to retreat patients that have previously responded to DD and that responses can be obtained in those with low CD25 expression [105,107].

### What are the effects of novel agents that interfere with gene expression?

#### Histone deacetylase inhibitors

##### Efficacy

The histone deacetylase inhibitors (HDACis) vorinostat and romidepsin are novel agents that increase acetylation of histones and other proteins leading to tumor suppressor gene transcription, inhibition of tumor cell growth and apoptosis.

There are no RCT's. A nonrandomized phase II trial of vorinostat was performed at three dosing schedules. Thirty-three patients were enrolled, a PR was obtained in eight patients (median time to response 11.9 weeks, median response duration 15.1 weeks). Relief of pruritus was obtained in 45% of patients. The dosing schedule of 400 mg daily was selected as the most beneficial [109]. In a further phase IIb study of 74 patients with stage IB–IVA disease (61 with IIB or greater), OR (measured by mSWAT) was 29.7% (median time to response 56 days, median time to progression 4.9 months) [110]. Two years following enrolment, six of 74 patients remained on vorinostat (five with continued response and one with SD), providing evidence for its long-term safety and tolerability [111].

In a single-arm, phase II, open-label multinational study of intravenous romidepsin in 96 patients (71% with advanced disease) there was an OR of 34% with six CRs (38% with advanced disease, including five CRs). The median time to response was 2 months and median duration of remission was 15 months. Improvement in

pruritus was noted in 28 of 65 patients (43%), including patients with no objective clinical response [112].

In a phase II multicenter study of 71 patients (87% with advanced disease), there was an OR of 34% with four CRs. Median duration of response was 13.7 months [113].

##### Drawbacks

Adverse effects include nausea, vomiting, fatigue, thrombocytopenia, and granulocytopenia.

##### Comments

Both HDACis have FDA approval in the USA for use in patients with persistent, progressive, or recurrent disease and have failed two prior systemic therapies. They are not currently licensed in Europe but can be obtained on a compassionate basis in patients who have exhausted all other treatment options.

#### Bortezomib

##### Efficacy

A phase II trial of the proteasome inhibitor bortezomib in patients with relapsed or refractory CTCL demonstrated an OR of 67% (17% CR, 50% PR) in 12 patients (10 CTCL, two peripheral T-cell lymphoma (PTCL) with only skin involvement) [114].

##### Drawbacks

Adverse effects included neutropenia, thrombocytopenia, and sensory neuropathy.

##### Comments

Larger studies are needed in order to establish its clinical role.



## What are the effects of radiotherapy in mycosis fungoides and Sézary syndrome?

### Superficial radiotherapy

#### Efficacy

No systematic reviews or RCTs were identified. Dose–response studies have established that localized superficial radiotherapy is an effective palliative therapy for individual lesions in MF [115]. A retrospective study of palliative superficial radiotherapy used to treat 191 lesions from 20 patients with MF showed CRs of 95% for plaques and small (<3 cm) tumors and a CR of 93% for large tumors (>3 cm), irrespective of dose. However, in-field recurrences within 1–2 years were more common for lesions treated with lower doses (42% for <10 Gy, 32% for 10–20 Gy, 21% for 20–30 Gy, and 0% for >30 Gy).

In a more recent study, 31 patients with MF were treated at 82 symptomatic sites. Initially, patients were treated with 4 Gy in two fractions (17 lesions); however, 70% of the lesions failed to respond. Increasing the dose to 8 Gy in two fractions yielded a CR of 92% (60 of 65 lesions) [116].

#### Drawbacks

Superficial radiation is well tolerated. Mild local erythema and occasional erosion have been reported. Use of low-dose/energy (8 Gy in two or three daily fractions at 80–150 kV) is therapeutically effective and allows treatment of overlapping fields and lower limb sites.

#### Comments

CTCL is highly radiosensitive, and localized superficial radiotherapy is an invaluable treatment for patients with all stages of MF. Treatment should be palliative except for patients with solitary localized disease, in whom a “cure” is theoretically possible. The use of high-dose fractionation regimens for individual lesions should be avoided because the CRs are similar to those for low-dose regimens (see above) and recurrent disease adjacent to previously treated fields can be treated with overlapping fields if necessary. Treatment of disease on the lower legs can be difficult, in view of a higher risk of radiation necrosis with repeated treatments.

### Total skin electron beam therapy

#### Efficacy

A systematic review of mostly retrospective studies of TSEB therapy as monotherapy for 952 patients with all stages of CTCL has established that response is dependent on the stage of disease, skin surface dose, and energy, with CRs of 96% in stage IA/IB/IIA disease, 36% in stage IIB disease, and 60% in stage III disease [117]. Greater skin surface dose (32–36 Gy) and higher energy (4–6 MeV) were significantly associated with a higher CR; 5-year relapse-free survivals of 10–23% were noted [117].

One small RCT has compared TSEB therapy with topical mechlorethamine in 42 patients, with similar CRs and response durations in both groups in early stages of disease, but better overall responses in later stages of disease with TSEB therapy [118].

A retrospective study of TSEB therapy (median dose 32 Gy; median treatment time 21 days) as monotherapy for 45 patients with erythrodermic CTCL (stage III–IVB) showed a CR of 60% with 26% disease free at 5 years [119]. The overall median survival was 3.4 years, which was associated significantly with an absence of peripheral blood involvement (stage III disease). Higher CRs (74%) and rates of disease-free progression (36%) were noted in patients receiving a more intense regimen (32–40 Gy and 4–6 MeV).

A retrospective study of 66 CTCL patients (1978–1996) treated with 30 Gy in fewer fractions (12 fractions over 40 days) showed a CR of 65%, with PFS of 30% at 5 years and 18% at 10 years [120]. Responses, and specifically the 5-year overall survival, were highest in those with early-stage disease (79–93% for IA/IB/III compared with 44% for IIB/IVA/B).

Several reports have described multiple courses of TSEB therapy in CTCL [121,122]. A retrospective analysis of 15 patients (1968–1990) with MF who received two courses of TSEB therapy reported a mean dose of 32.6 Gy for the first course and 23.4 Gy for the second, with a mean interval of 41.3 months. The CR for the second course was lower (40% compared with 73%) with no additional toxicities [121]. A study of 14 patients reported a mean dose of 36 Gy for the first course (93% CR) and 18 Gy for the second course (86% CR) [122]. Five patients received a third course (total dose 12–30 Gy). The median duration of response was 20 months for the first course and 11.5 months for the second course. No additional toxicities were reported. In both studies, the fractionation regimens employed may have been critical for tolerability (1 Gy per day at 6 MeV over 9–12 weeks).

In a retrospective study, 141 patients received TSEB therapy with a mean total dose of 30 Gy. The OR was 94.7%. In those with T1 and T2 disease (57) the CR was 87.5% and 84.8% respectively, and 54.4% relapsed within 1 year. Eighteen received a second course; the remaining 13 patients were treated with other modalities, including topical steroids, PUVA, and topical or systemic chemotherapy. The 5-year freedom from relapse was 70% compared with 39% for the other treatment modalities combined [123].

Similar response rates and durations have been reported with lower doses of TSEB therapy. A retrospective study of 102 patients (stage T2 51, T3 29, T4 22) were treated in three different dosage groups (5 to <10 Gy, 10 to <20 Gy, and 20 to <30 Gy). The overall response (>50% improvement) was 90% in the low-dose group compared with 98% and 97% in the other two groups respectively. There was no significant difference in median PFS in the T2 and T3 patients when stratified by dose group, and PFS in each group was comparable to patients that had received the standard dose of 30–36 Gy [124].

A prospective phase II study evaluated low-dose TSEB therapy (10 Gy) in 10 patients with stage IB–IV MF (four fractions of 1 Gy weekly to a total dose of 10 Gy). The OR was 90% with a CR or very good PR (<1% skin affected) of 70% and median response duration of 5.2 months [125].

### Combination total skin electron beam therapy regimens

An RCT that included 103 CTCL patients in which TSEB therapy and multiagent chemotherapy (CAVE: cyclophosphamide, Adriamycin, vincristine, and etoposide) was compared with sequential topical therapy, including superficial radiotherapy and phototherapy, reported a higher CR in the TSEB therapy/chemotherapy group (38% compared with 18%;  $P = 0.032$ ), but after a median follow-up of 75 months, the disease-free survival and overall survival did not differ significantly [126].

A retrospective study comparing TSEB therapy (32–40 Gy) alone with TSEB therapy followed by ECP (given 2 days monthly for a median of 6 months) in 44 patients with erythrodermic MF/SS (57% stage III, 30% stage IVA, 13% stage IVB; overall, 59% had B1 hematological involvement) has reported a CR of 73% after TSEB therapy, with a 3-year disease-free survival of 49% for 17 patients who received only TSEB therapy (overall survival 63%) and 81% for 15 patients who received TSEB therapy followed by ECP (overall

survival 88%) [127]. A multivariate analysis suggested that the combination of TSEB therapy and ECP was significantly associated with a prolonged disease-free and cause-specific survival when corrected for peripheral blood involvement (B1) and stage of disease.

### Drawbacks

Adverse effects of TSEB therapy include radiation-induced secondary cutaneous malignancies, telangiectasia, pigmentation, anhidrosis, pruritus, alopecia, and xerosis.

### Comments

EORTC consensus guidelines for TSEB therapy use in CTCL have been published [128].

Although these studies are uncontrolled and mostly retrospective, response rates indicate that TSEB therapy is highly effective for CTCL. Lower doses of TSEB therapy show similar response rates, are associated with fewer side effects, and allow further treatment courses to be given at relapse.

An RCT in CTCL indicates that combined TSEB therapy and chemotherapy is no more effective than sequential skin-directed therapy. Studies of low-dose TSEB therapy alone and in combination with newer agents are ongoing.

The data on long-term disease-free survival and overall survival in erythrodermic CTCL suggest that TSEB therapy is effective, particularly if combined with ECP, but this requires confirmation in an RCT.

## What are the effects of single-agent chemotherapy in mycosis fungoides/Sézary syndrome?

### Single-agent chemotherapy regimens

#### Efficacy

No RCTs have been reported. A systematic review of uncontrolled open studies of single-agent regimens in 526 CTCL patients (1988–1994) revealed ORs of 62%, with a CR of 33% and median response durations of 3–22 months [83]. These therapies included alkylating agents (chlorambucil and cyclophosphamide), antimetabolites (methotrexate), vinca alkaloids, and topoisomerase II inhibitors.

### Drawbacks

Infection and myelosuppression are significant risks.

### Comments

The lack of controlled studies makes interpretation difficult, but single-agent regimens may have similar efficacy to combination regimens (see below) with lower toxicity and may be preferable as palliative therapy in late stages of MF and SS as durable responses and cures are rarely achieved.

### Methotrexate and trimetrexate

#### Efficacy

A retrospective report of low-dose methotrexate in 29 patients with erythrodermic CTCL (III/IVA) has shown a 41% CR, with an OR of 58% [129]. Median freedom from treatment failure was 31 months and overall survival was 8.4 years. Weekly doses ranged from 5 to 125 mg for a median duration of 23 months. Trimetrexate, a lipophilic antifolate that diffuses passively into cells and is therefore less prone to drug resistance, was assessed in an open trial of 20 patients with refractory/resistant CTCL (three ALCL, 15 MF or SS with large-cell transformation in 14, two PTCL) using a schedule

of 200 mg/m<sup>2</sup> every 14 days for up to 12 doses. There was an OR of 45% (one CR, eight PR), including two patients who had previously been resistant to methotrexate [130].

### Drawbacks

Adverse effects in the methotrexate trial included reversible abnormalities of liver function, mucositis, cutaneous erosions, reversible leukopenia and thrombocytopenia, nausea, diarrhea, and in one case pulmonary fibrosis. Trimetrexate has a similar pattern of adverse effects and appears to be well tolerated.

### Comments

Although these data are uncontrolled, the overall survival in the methotrexate study is surprisingly good. A randomized study comparing methotrexate with other single-agent chemotherapies in erythrodermic CTCL would be worthwhile. The use of trimetrexate in CTCL merits further investigation.

### Pralatrexate

Pralatrexate is emerging as a promising new agent in the treatment of CTCL.

#### Efficacy

Twelve patients with transformed MF were included in a phase II study of pralatrexate (30 mg/m<sup>2</sup> per week for 6 weeks of a 7-week cycle) in patients with PTCL. The OR was 25% [131].

In a phase II study of 29 patients with heavily pretreated CTCL (15 mg/m<sup>2</sup> per week for 3 weeks out of every 4 weeks) the median number of cycles was four and the OR was 45% (evaluated by the mSWAT tool) [132].

### Drawbacks

Adverse effects include mucositis, leukopenia, thrombocytopenia, and anemia.

### Comments

The lower dose was well tolerated, with reduction in adverse effects, including mucositis.

### Purine analogues

#### Efficacy

A systematic review of purine analogues in CTCL (1988–1994) revealed respective ORs and CRs of 41% and 6% for deoxycoformycin ( $n = 63$ ), 41% and 19% for 2-chlorodeoxyadenosine ( $n = 27$ ), and 19% and 3% for fludarabine ( $n = 31$ ) [83]. Most studies included patients with PTCLs. No comparative studies were available.

A prospective open study of deoxycoformycin at starting doses of 3.75–5.0 mg/m<sup>2</sup> per day for 3 days every 3 weeks, in 28 heavily pretreated patients, of whom 21 had CTCL (14 with SS, seven stage IIB) revealed an OR of 71%, with 25% CR and 46% PR. The response was short-lived (median duration 2 months for stage IIB, 3.5 months for SS), except in two cases of SS, with remissions for 17 and 19 months [133].

Two open studies of deoxycoformycin in patients with CTCL (27 MF and 37 SS) have shown ORs of 35–56%, with CRs from 10 to 33% and a median disease-free interval of 9 months in one of the studies [134,135]. Responses were better in SS than in MF.

Combination therapy consisting of deoxycoformycin and interferon alpha in CTCL has shown ORs and CRs of 41% and 5%, respectively [136].

A phase II trial of 2-chlorodeoxyadenosine in 21 refractory CTCL patients (MF IIB/IV and SS) revealed an OR of 28%, with a 14% CR (median duration of 4.5 months) and a 14% PR (median duration 2 months) [137].

#### **Drawbacks**

Side effects include nausea, infections (especially herpetic), CD4 lymphopenia, renal toxicity, hepatotoxicity, and myelosuppression (especially for 2-chlorodeoxyadenosine and fludarabine).

#### **Comments**

Although efficacy in CTCL is moderate, most patients were heavily pretreated and relatively chemoresistant. Patients with SS appear to respond better. Purine analogues are appropriate as monotherapy, especially in SS, but the response duration may be short. Comparative trials with other single-agent regimens in SS are required.

### **Gemcitabine**

#### **Efficacy**

A phase II prospective trial (1200 mg/m<sup>2</sup> weekly for 3 weeks each month for three cycles) in 44 previously treated patients with CTCL (30 MF stage IIB or III) reported a PR of 59% and a CR of 12%, with median durations of 10 months and 15 months, respectively [138]. A phase II prospective trial in 32 patients with either CTCL (26 MF, one SS) or PTCL (five) treated with 1200 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle for six cycles revealed seven (22%) CRs and 17 (53%) PRs, with a median duration of CR of 10 months [139].

#### **Drawbacks**

The treatment was well tolerated with only mild hematological toxicity.

#### **Comments**

Gemcitabine is a pyrimidine analogue that is well tolerated in heavily pretreated patients with advanced stages of MF. Further trials are required.

### **Doxorubicin**

#### **Efficacy**

A phase II prospective, multicenter study of pegylated liposomal doxorubicin (20 mg/m<sup>2</sup> at days 1 and 15 every 28 days for six cycles) in 40 heavily pretreated patients with stage IIB, IVA, or IVB disease showed a CR of 6.1% and a PR of 34.7% using global response criteria. However, 60.5% of patients had >50% reduction in skin manifestations. The median time to progression was 7.4 months and the median duration of response was 6 months. There were two early deaths: one from cardiovascular toxicity and another from disease progression [140].

A second multicenter, prospective study of objective response to pegylated liposomal doxorubicin (40 mg/m<sup>2</sup> once every 4 weeks for up to eight cycles) in 25 patients with stage II–IV CTCL (who had failed to respond to two previous lines of therapy or who had histologically transformed epidermotropic disease) showed an OR of 56% (five CR, nine PR). The median PFS from end of treatment was 5 months. The higher dose of 40 mg/m<sup>2</sup> did not improve efficacy but did increase toxicity [141].

An open study of pegylated liposomal doxorubicin (20 mg/m<sup>2</sup> monthly to a maximum of 400 mg or eight cycles) in 10 patients with MF, revealed a CR in six patients and a PR in two patients,

with a median response duration of 15 months [142]. A retrospective study of 34 patients with CTCL treated with variable doses of pegylated liposomal doxorubicin, 20–40 mg/m<sup>2</sup> (26 received 20 mg/m<sup>2</sup>) every 2–4 weeks for eight cycles, revealed an OR of 88% (15 CR, 15 PR) [143].

#### **Drawbacks**

Hematological toxicity and infectious complications were reported. Palmoplantar erythrodysesthesia occurred rarely.

#### **Comments**

Pegylated liposomal doxorubicin is an effective and well-tolerated chemotherapeutic agent in CTCL.

### **Temozolamide**

#### **Efficacy**

There is one multicenter phase II trial of 26 patients with heavily pretreated MF (stages IB–IVB) at a dose of 200 mg/m<sup>2</sup> for 5 days every 28 days. The OR was 27% (8% CR, 19% PR) and the median disease-free survival was 4 months [144].

#### **Drawbacks**

Adverse events include hematologic, gastrointestinal, and constitutional toxicity.

#### **Comments**

Temazolamide is an oral derivative of dacarbazine, which enables easier administration and reduces hospital visits. Further studies are required to establish its efficacy.

### **What are the effects of multiagent chemotherapy regimens in mycosis fungoides and Sézary syndrome?**

#### **Combination chemotherapy**

#### **Efficacy**

A systematic review of all systemic therapy in CTCL (1988–1994) showed an OR of 81% in 331 patients treated with different combination chemotherapeutic regimens, with a CR of 38% and response duration ranging from 5 to 41 months, with no documented cures for patients with late stages of disease (IIB–IVB) [83].

Prospective nonrandomized studies of different multiagent chemotherapy regimens have revealed similar ORs. A combination of idarubicin, etoposide, cyclophosphamide, vincristine, prednisolone, and bleomycin (VICOP-B) was used to treat 25 CTCL patients (eight stage IIB, 13 stage IVA, four stage IVB) for 12 weeks. An OR of 80% with 36% CRs were documented, although 10 patients were treatment naive. The two patients with SS did not respond, and median response duration in patients with MF was 8.7 months. Stage IIB patients had a median duration of response of 22 months, but four previously untreated patients received additional TSEB therapy after completion of chemotherapy [145].

A combination of etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisolone (EPOCH) was used to treat 15 patients with advanced, refractory CTCL (six SS; four stage IVB MF; one ATLL and four ALCL). After a median of five cycles, 27% had a CR and 53% achieved a PR, with an overall median survival of 13.5 months [146].

#### **Drawbacks**

Multiagent chemotherapy regimens are associated with very high rates of toxicity and morbidity, including nausea, anorexia,

infection, hepatotoxicity, and myelosuppression. Patients with CTCL are at high risk of septicemia, and therapy-related mortality is a significant risk.

### Comments

Patients with late stages of CTCL (IIB–IVB) will require treatment with a chemotherapy regimen, although the response duration is short. However, as overall survival rates are unchanged and toxicity may be considerable, these regimens are usually reserved for patients with extensive lymph node and visceral disease. Single-agent regimens appear to have similar efficacy, although studies involving a comparison between single-agent and multiagent regimens, with or without TSEB therapy, are required. Further well-designed studies of maintenance/adjuvant treatment with bio-immunotherapy, SDT or TSEB therapy for patients achieving a response with chemotherapy are required as patients frequently relapse with early-stage disease and there is currently no trial evidence that this approach improves outcome.

### Myeloablative chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation

#### Efficacy

No RCTs were identified. Most studies were based on small numbers of patients. High-dose chemotherapy with TSEB therapy and total-body irradiation (TBI) in seven patients with MF (two patients had both TSEB therapy and TBI), followed by autologous bone-marrow transplantation in six patients (three stage IIB, one stage IVA, two stage IVB) produced five CRs, but three patients relapsed within 100 days [147]. The other two patients were disease free at almost 2 years.

High-dose chemotherapy combined with either TSEB therapy or TBI and followed by autologous peripheral blood stem-cell transplantation in nine patients with stage IIB/IVA MF revealed CRs in eight patients and durable clinical responses in four patients (median disease-free survival 11 months) [148].

A recent retrospective study of AHSCT included a heterogeneous group of 60 patients (36 MF and 15 SS) who received both myeloablative and reduced-intensity conditioning (RIC) regimens (45 matched related donor (MRD), 15 matched unrelated donor (MUD)) with an estimated 1-year survival of 66%, falling to 54% at 3 years [149]. RIC was associated with a decreased nonrelapse mortality without an increase in relapse/progression. MRD transplant patients had a better PFS and overall survival than those with an MUD. The risk of relapse was increased in patients who had undergone T-cell depletion. The transplant-related mortality at 1 year was 25%.

Another report described outcomes in 19 patients with advanced refractory CTCL who underwent an RIC regimen that included TSEB therapy, followed by allogeneic transplant using fludarabine/melphalan conditioning in 16 of the patients, with thymoglobulin for mismatched donors. Eighteen patients engrafted and one died of sepsis in the immediate posttransplant period. Fifteen reached full donor chimerism, 12 developed acute graft versus host disease (GvHD), and 12 developed chronic GvHD. The overall intent-to-treat response rate was 68% with a CR of 58%. Six patients died (two bacterial sepsis, one lung cancer, one chronic GvHD and fungal infection, and two PD). Skin relapse occurred in eight patients, five of whom had a CR with reduction of immunosuppression and donor lymphocyte infusions. Eleven patients remained in remission with a median follow up of 19 months [150].

### Drawbacks

Autologous-HSCT appears to be associated with only short-term remission and is therefore difficult to justify despite the limited data. Myeloablative AHSCT is associated with a high incidence of toxicity and systemic infections, and there is significant mortality. There is less toxicity with nonmyeloablative regimens, allowing treatment of older patients and those with comorbidities. The risk of life-threatening infection is lower with RIC allografts. Data available suggest that T-cell depletion with Alemtuzumab is associated with a higher rate of relapse and transplant-related mortality and should not be used in the conditioning regimen [149].

### Comments

AHSCT is successful in part because of the graft-versus-lymphoma effect of the donor graft, independent of the conditioning regimen, but this has to be balanced against the morbidity associated with chronic GvHD [150]. Maximal benefit from RIC-AHSCT is observed when performed before patients develop highly refractory disease and when there is low disease bulk at the time of transplantation [150]. Clinical trials to identify the optimal clinical conditioning regimen and timing of AHSCT in the course of the disease are required.

### Key points

- Although there are few well-designed RCTs in CTCL, there is evidence from uncontrolled studies that SDTs have a significant therapeutic effect and are the standard of care in patients with early-stage MF (IA–IIA).
- Patients with stage IA disease can have a normal life expectancy, and so aggressive therapies with a significant mortality and morbidity should be avoided, especially when the chance of a cure is very low.
- Patients with early-stage disease (IA/IB/IIA) should be offered SDTs such as topical mechlorethamine, phototherapy, PUVA, and superficial radiotherapy. Combinations of interferon alpha, bexarotene, or TSEB therapy should be considered for patients with persistent or recurrent stage IB/IIA disease. Some patients with stage IA disease may not require any specific therapy.
- Patients with late stages of disease (IIB/IV) should be offered TSEB therapy, single-agent palliative chemotherapy, and multiagent chemotherapy, according to performance status. Patients should be offered entry into a well-designed clinical trial if available.
- Patients with erythrodermic disease should be offered ECP, immunotherapy, alemtuzumab, and single-agent chemotherapy as palliative therapy, aiming to improve quality of life. TSEB therapy may be indicated for erythrodermic disease when there is a lack of significant peripheral blood tumor burden. Entry into a clinical trial should be offered, if available.
- In late-stage disease, adjuvant maintenance therapy should be offered where possible.
- The role of RIC-AHSCT in patients with advanced disease needs further study.

### Recommendations for the future

- New topical therapies should be assessed in the context of well-designed clinical trials.
- The role of new immunotherapies in early-stage (IB/IIA) disease should involve comparative RCTs with standard therapies.
- Future clinical trials in advanced disease (IIB–IV) are required to address the urgent need to improve overall survival, and future trials should also address a need to improve duration of response without increasing toxicity after PUVA and TSEB therapy.
- The role of RIC-AHSCT in patients with advanced disease needs further study.



## Abbreviations

AHSCT	allogeneic hematopoietic stem cell transplant
5-ALA	5-aminolevulinic acid
ALCL	primary cutaneous anaplastic large cell lymphoma
ATLL	HTLV-1 associated adult T-cell leukemia/lymphoma
BCNU	1,3-bis (2-chloroethyl)-1-nitrosourea
CR	complete response
CTCL	cutaneous T-cell lymphoma
DD	denileukin diftitox
ECP	extracorporeal photopheresis
EPOCH	etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisolone
EORTC	European Organisation for the Research and Treatment of Cancer
FDA	United States Food and Drug Administration
FFR	freedom from recurrence
GvHD	graft versus host disease
HDACi	histone deacetylase inhibitor
HTLV-1	human T-lymphotropic virus type-1
IFN	interferon alpha
ISCL	International Society for Cutaneous Lymphomas
MF	mycosis fungoides
mSWAT	modified severity weighted assessment tool
NR	not recorded
OR	overall response
PD	progressive disease
PFS	progression free survival
PR	partial response
PTCL	peripheral T-cell lymphoma
PUVA	psoralen + ultraviolet A light
RCT	randomized clinical trial
RIC	reduced intensity conditioning
SD	stable disease
SDT	skin-directed therapy
SS	Sézary syndrome
TSEB	total skin electron beam
TBI	total body irradiation
UVB	ultraviolet B light
VICOP-B	Idarubicin, etoposide, cyclophosphamide, vincristine, prednisolone, and bleomycin

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# Actinic keratosis and Bowen's disease

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## Background

### Definition

Actinic keratoses (AKs), also known as solar or senile keratoses, and Bowen's disease (BD) are precursors of invasive squamous cell carcinoma (SCC). Whereas AK is precancerous, BD represents intraepidermal (in situ) SCC [1]. There is some evidence that AK lesions can be precursors to not only SCC but also to basal cell carcinomas [2]. AK presentation is characterized by multiple, erythematous, scaly papules that may be pink, red, or brown in color. AK lesions are typically less than 1 cm in diameter [3,4]. AK is termed "actinic cheilitis" or "solar cheilitis" if the lips are involved. BD usually presents as a solitary, well-demarcated, erythematous plaque of varying size, with irregular borders and a crusted, scaling, or fissured surface, usually persistent and enlarging (Figures 35.1 and 35.2) [5].

AK arises on areas of intense ultraviolet light exposure, with over 80% developing on the head and neck, forearms, and hands [6–8]. A male predominance is observed [4,9]. Other contributing factors include skin type, age, sun exposure, latitude, and ozone integrity [3,4]. The distribution of BD varies, demonstrating predominance on the lower legs in women and on the head and neck in men in the UK and Australia [10–12]. Australia and Denmark feature a marginal propensity of BD for women (56%) and occurrence on the head and neck (44–54%) [12,13]. Approximately one-third of patients with BD have other nonmelanoma skin cancers at diagnosis [13].

### Incidence/prevalence

The exact incidence and prevalence of AK and BD are unknown. Both increase in prevalence with advancing age [3,12,14,15]. AK may occur in children with albinism and xeroderma pigmentosum [16].

### Etiology

Chronic solar damage is the principal etiological factor in AK and BD [12,17–19]. People with light complexions, blue eyes, and childhood freckling are at highest risk, given their innate lack of protec-

tive pigment [6]. Individuals with compromised immunity (such as organ-transplant recipients), with diminished or absent melanin (such as albinos), and with decreased capacity to repair ultraviolet-induced damage (such as persons with xeroderma pigmentosum) all demonstrate an increased risk for AK. Risk factors for BD include arsenic exposure [20–23], immunosuppression [24], radiation, chronic injury, and human papillomavirus (HPV), particularly HPV-16 in anogenital lesions [25,26].

### Prognosis

Although the condition is precancerous [27,28], the probability of a given AK undergoing malignant transformation is unknown [15]. The reported risk of progression to SCC for individual lesions ranges from less than 1% to 16% per year [29]. The 10-year risk of malignant transformation of at least one AK on a given patient is 10% [30]. The relative risk of malignant transformation depends ultimately on factors related to the AK itself (for example, thickness), as well as patient characteristics (for example, drug therapy, degree of pigmentation, immune status) [4]. However, another aspect that may confound estimation of the prognosis of AK is the spontaneous regression rate. A study from Queensland [31] reported a spontaneous regression rate of 85% (95% confidence interval [CI], 75–96%) in people with prevalent AK (AK diagnosed on a person during the first examination) and 84% (95% CI, 72–96%) in persons with incident AK (AK appearing for the first time during the study). However, the distribution of lesions per person was highly skewed, with 12% of study participants having 65% of the total number of AKs. In the Veteran's Affairs topical tretinoin chemoprevention trial, the risk of progression from AK to primary SCC at 4 years was 2.6%, and the risk of progression from AK to primary BCC was 1.6% at 4 years [2].

BD is associated with an excellent prognosis, related to the disease's indolent nature and its favorable response to a range of therapies. Although there is no recent literature on the risk of BD progression to invasive SCC, older studies suggest the risk is 3–5% if lesions are left untreated [32,33]. Contrary to the findings of earlier reports [34–37], a meta-analysis of 12 studies in 1989 determined no significant association between BD and internal malignancy [38].



Figure 35.1 Actinic keratosis.

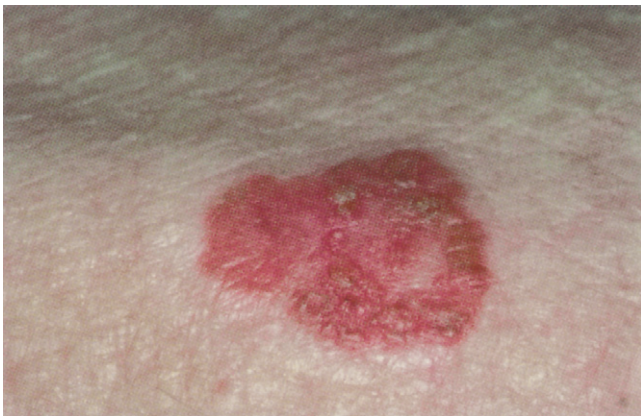


Figure 35.2 Bowen's disease.

### Aims of treatment

The aims of treatment are to achieve clinical and histological clearance, prevent progression to invasive SCC, prevent recurrence, achieve cosmetic improvement, and minimize adverse effects of treatment. One unique aspect of AK treatment is the decision to utilize spot versus field treatment, the former to focus on visible discrete lesions and the latter to treat an area that may have sub-clinical lesions. The studies reviewed below primarily focus on field treatment.

### Relevant outcomes

- Short-term clinical and histological clearance.
- Recurrence rates (these should be calculated at least 1 year following treatment, in order to assess the recurrence of AK and BD lesions adequately).
- Prevention of SCC.
- Adverse effects of treatment.

### Methods of search

Previously, a Medline search from 1966 to the end of December 2006 was performed to identify studies of 5-fluorouracil (5-FU) and cryotherapy in patients with AK. We also previously searched non-5-FU and non-nitrogen therapies by name and type, as well as the term "actinic keratosis treatment." In order to update this search,

we searched Medline and Embase from January 2007 to July 2012 using the same search methods. We scrutinized review articles for treatments not detected through database searches.

We limited the topic to non-anogenital BD and to publications written in English, since we did not have ready access to translation facilities. We reported numbers of patients as well as number of lesions treated wherever information was available. Studies that used patients as the unit of randomization (which makes the best clinical sense) were preferred over studies that used lesions as the unit of randomization without adjusting for a person effect.

Since few randomized controlled trials (RCTs) were found, uncontrolled trials were included in this chapter, with the exception of studies that had fewer than 10 patients, unless they were the only available studies. Currently, there is no available Cochrane review available; however, data are currently being collected for "Interventions of actinic keratoses." Evidence was graded using the quality-of-evidence scale employed the strength of recommendation taxonomy (SORT) criteria [39]. We have only presented data from the best-quality studies; for example, data from comparative studies are presented preferentially over data from case series when both exist for a given intervention.

## Questions

### What are the effects of non-drug therapy?

#### Cryotherapy

Cryotherapy involves delivering liquid nitrogen to affected areas with a spray device or cotton tip applicator. The mechanism of action of cryotherapy involves rapid cooling, resulting in intracellular ice crystal formation, followed by a slow thaw that results in cell damage [40]. Additional cycles lead to more damage. Since cryotherapy has been a longstanding mainstay of the treatment of AKs and BD, newer treatments have utilized cryotherapy as a comparison arm. We will discuss some of these comparisons in this cryotherapy section as well as in the other treatment sections below.

#### Actinic keratoses (strength of recommendation: A)

We evaluated one systematic review [41] and five RCTs (Table 35.1) [42–46]. All five RCTs were comparative studies. Two nonrandomized, uncontrolled studies investigating the effects of freeze time and temperature are also discussed [47].

**Benefits** The percentage of lesions that completely resolved with cryotherapy ranged from 66 to 88% in the five RCTs reviewed, although follow-up time varied between 3 months and 1 year. A single treatment with cryotherapy results in lesion response rates of 68–76% [42–44], while the response rate of lesions retreated at 3 or 6 months increased to 86–87% [42,45].

A nonrandomized, uncontrolled study found that the freeze duration may influence the success of cryotherapy treatment [47]. Complete responses in lesions with freeze times greater than 5 s were higher than responses for lesions with freeze times less than 5 s (69% compared with 39%). The complete response rate for lesions with freeze times greater than 20 s was 83% at 3-month follow-up [47]. Freeze temperature may affect outcome as well. A small, non-randomized study of 36 patients with 180 AKs found a 100% cure rate at 6 weeks when lesions were treated to a skin surface temperature of  $-5^{\circ}\text{C}$  using an integrated, infrared sensor [48].

The single study examined in the systematic review treated a total of 1018 lesions in 70 patients. Clinical follow-up after treatment

**Table 35.1** Summary of 5 RCTs using cryotherapy to treat AKs.

First author, ref	Intervention	Comparators	Study design	Study population	Sample size (n)	Outcome measures	Main results	Adverse effects	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Kaufmann (2008) [45]	1–2 treatments with 2 FTCs	MAL–PDT	RCT	Multiple AKs	121 1343 AKs	Percentage reduction in lesions at 24 weeks	Cryo 88% vs MAL–PDT 76%	“Cold-exposure injury”	Adequate Not adequate Adequate
Morton (2006) [42]	1–2 treatments with 2 FTCs	MAL–PDT	RCT	Multiple AKs on face/scalp	119 1501 AKs	Percentage reduction in lesions at 24 weeks	Cryo 86% vs MAL–PDT 89%	“Cryotherapy reaction”, not otherwise specified	Adequate Not adequate Adequate
Freeman (2003) [43]	1 treatment with 1 FTC	MAL–PDT and placebo–PDT	RCT	Multiple AKs on face/scalp	204 855 AKs	Percentage reduction in lesions at 3 months	Cryo 68% vs MAL–PDT 91% vs placebo 30%	Not addressed	Adequate Not adequate Not adequate
Szeimies (2002) [44]	1 treatment with 2 FTCs	MAL–PDT	RCT	Multiple AKs	193 699 AKs	Percentage reduction in lesions at 3 months	Cryo 75% vs MAL–PDT 69%	Burning sensation, pain, crusting	Adequate Not adequate Not adequate
Foley (2011) [46]	1–4 treatments	5% imiquimod	RCT	Multiple AKs on face/scalp	71 710 AKs	Percentage reduction in lesions at 12 months	Cryo 85% vs imiquimod 67%	Hypopigmentation, blistering, erythema, flaking/scaling/dryness, scabbing/crusting	Adequate Not adequate Unknown

FTC: freeze–thaw cycle; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

<sup>a</sup>Adequate if clear description of method of randomization and concealment of allocation of randomization.

<sup>b</sup>Adequate if assessors and participants were completely blinded to the study interventions.

<sup>c</sup>Adequate if an intention-to-treat analysis was carried out.

ranged from 1 to 8.5 years. Twelve recurrences were reported, giving a success rate of 99% during a follow-up period of 1–8.5 years [49].

**Harms** Adverse events associated with cryotherapy treatment include stinging, pain, or a burning sensation, erythema, edema of the skin, hyperpigmentation or hypopigmentation, blistering, skin infection, crusting, itch, and peeling [43,50]. However, the majority of events are of mild to moderate severity, are well tolerated, and are of short duration [44,50]. The percentages of patients who reported local adverse reactions after a single cryotherapy treatment ranged from 26 to 72% [42,44,45]. One study reported that 55% of patients treated with cryotherapy had clinically evident hypopigmentation at 12 months [46]. Unfortunately, the longer the duration of freezing, the more likely it is that an adverse event will occur. Very aggressive freezing may lead to a large blister, ulceration, longer healing times, more postoperative pain, and more pigimentary changes [51].

**Comment** Cryotherapy continues to be a popular and effective treatment for isolated AKs. Consideration should be given to the duration of treatment, since longer freeze times result in a greater response. Longer freeze times should particularly be used for larger lesions or those that are more hyperkeratotic. Cosmetic outcome remains a concern for both physicians and patients for cryotherapy: two RCTs investigating intraindividual methyl aminolevulinate (MAL) photodynamic therapy (PDT) and cryotherapy reported that only 21–22% of patients preferred cryotherapy as a treatment modality [42,45].

### **Bowen's disease (strength of recommendation: A)**

We found no systematic reviews and one RCT. The RCT was a comparison of cryotherapy ( $n = 20$  lesions) with PDT ( $n = 20$  lesions) [52]. One quasi-RCT compared the efficacy of MAL–PDT ( $n = 96$ ), placebo–PDT ( $n = 17$ ), cryotherapy ( $n = 82$ ), and fluorouracil ( $n = 30$ ) [53]. The patients were randomized to MAL–PDT, placebo, or standard therapy. The standard therapy was either cryotherapy ( $n = 82$ ) or 5-FU ( $n = 30$ ), chosen by the treating investigator. One unblinded controlled trial compared cryotherapy ( $n = 36$ ) with curettage ( $n = 44$ ) [54], and one retrospective study compared cryotherapy ( $n = 82$ ) with external beam radiotherapy ( $n = 59$ ) [55].

**Benefits** Across studies, PDT was superior to cryotherapy in the acute clearing of lesions after a single treatment. In addition, PDT had a lower recurrence rate with fewer adverse side effects [52,53]. Complete clinical clearance was comparable between cryotherapy (94% with one treatment and 100% with two) and curettage (100% after one treatment) 1 week after treatment. Overall, the average time to healing was 60 days. Healing was significantly prolonged for lower leg lesions treated by cryotherapy in comparison with curettage (90 vs 30 days;  $P < 0.001$ ). No difference in healing time was observed for other sites. Recurrence rates were lower (12% vs 50%;  $P < 0.04$ ) and the time to recurrence was longer ( $P < 0.0087$ ) for curettage compared to cryotherapy [54].

**Harms** Complications of cryotherapy include pain, poor healing, and infection, requiring antibiotics [56]. Pain of mild to moderate severity was reported in 19 of 20 lesions during cryotherapy, which

was significantly higher than pain reported during PDT ( $P < 0.01$ ) [52]. Ulceration occurred in five of the 20 lesions, and two of the five patients concerned were later prescribed antibiotics for cellulitis developing around the lesions. Visible scarring in four of the 20 lesions was observed at 12 months posttreatment [52]. Patients were 10.4 times more likely to report pain with cryotherapy ( $P < 0.001$ ) and were 5.5 times more likely to report pain on the lower leg in comparison with other body sites, irrespective of the treatment method used ( $P < 0.016$ ) [54]. Poor healing occurred in 2% of patients who received cryotherapy in this retrospective comparison study with radiotherapy [55]. Biopsy of these poorly healing lesions revealed residual tumor. The authors speculated that failure to heal may suggest residual BD and may be an indication for surgical excision.

**Comment** These studies report high short-term clearance rates with liquid-nitrogen cryotherapy, although poor healing, as well as discomfort related to the procedure, may limit its utility in BD of such sites as the lower legs. In relation to the study comparing cryotherapy and curettage, methodological limitations include deviation from an intention-to-treat (ITT) analysis and use of nonrandom allocation. The former omission would tend to overestimate the efficacy of the intervention, whereas the latter would tend to weaken the validity of the results, as there is no assurance that known and unknown confounders are homogeneously distributed between the comparison groups. The treatment protocol in these studies varied on how aggressive the treatment was, thus making it difficult to determine the adequate amount of cryotherapy to attain the lowest recurrence rate. However, a more aggressive approach consisting of 20 s at least twice or 30 s at least once might yield better results.

### Laser treatment

Studies investigating ablative skin resurfacing with erbium–yttrium aluminum garnet (Er:YAG) laser for AK and BD highlight its capacity to selectively vaporize the epidermis and upper papillary layer with minimal scar formation. We found no systemic reviews for Er:YAG laser for either AK or BD, and no RCTs for BD.

Fractional photothermolysis is a nonablative or minimally ablative therapy which treats only fractions of the skin by inducing small areas of damage, referred to as “microscopic thermal zones.” The surrounding tissue is undamaged and allows for faster epidermal repair. Noncontact fractional photothermolysis, performed with the handpiece held several millimeters above the skin surface, is hypothesized to result in targeted damage in the epidermis and dermal–epidermal junction, resulting in a “quasi-ablative” effect. There are no RCTs for fractional photothermolysis of AK or BD.

### Actinic keratoses (strength of recommendation: B)

**Erbium–yttrium aluminum garnet and carbon dioxide lasers** The single RCT we reviewed was a comparison study between laser resurfacing with an Er:YAG laser and topical 5-FU in the treatment of AK [57]. In addition, we considered an uncontrolled prospective study as well as two retrospective reviews (Table 35.2) [58–60].

**Fractional photothermolysis** We reviewed two uncontrolled prospective trials investigating the use of fractional photothermolysis in AK. One trial examined the use of a 1550 nm fractionated erbium-doped fiber laser in the treatment of 348 AKs in 14 patients, using both clinical and histological endpoints at 3 and 6 months [61]. An additional uncontrolled trial investigated the use of

**Table 35.2** Summary of RCT and studies investigating ablative laser therapy to treat AKs.

First author, ref.	Intervention	Comparators	Study design	Study population	Sample size (n)	Outcome measures	Main results	Adverse effects	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Ostertag (2006) [57]	Er:YAG and/or CO <sub>2</sub>	5-FU	RCT	Multiple facial/scalp AKs	55	Percentage of patients with recurrent lesions within 1 year  Percentage reduction in lesions at 12 months	Er:YAG 41% vs 5-FU 81%  Er:YAG 91% vs 5-FU 77%	Erythema, edema, infection, acne, milia, hypopigmentation	Adequate Not adequate Adequate
Ostertag (2006) [60]	Er:YAG and/or CO <sub>2</sub>	None	Retrospective review	Multiple facial/scalp AKs	25	Percentage of patients with recurrent lesions at follow-up (7–70 months)	56%	Hypopigmentation, itching, atrophy, easy bruising	Not adequate N/A N/A
Iyer (2004) [59]	Er:YAG and/or CO <sub>2</sub>	None	Retrospective review	Multiple facial AKs	24	Percentage of patients with complete response at 1 year	88%	Erythema, infection, perioral scarring, transient hyperpigmentation, pseudo-hypopigmentation	Not adequate N/A N/A
Wollina (2001) [58]	Er:YAG	None	Uncontrolled prospective trial		29	Percentage of patients with complete response at 3 months	90%	None reported	Not adequate N/A N/A

<sup>a</sup>Adequate if clear description of method of randomization and concealment of allocation of randomization.

<sup>b</sup>Adequate if assessors and participants were completely blinded to the study interventions.

<sup>c</sup>Adequate if an intention-to-treat analysis was carried out.



noncontact fractional 1540 nm erbium/glass laser (Er:glass) in 17 patients with 3-month follow-up [62].

**Benefits of erbium–yttrium aluminum garnet** Combined data from the RCT and two retrospective studies suggest ablative laser therapy is very successful at reduction in AK burden, with a 91–94% decrease in numbers of AKs 1 year after treatment [57,59].

**Benefits of fractional photothermolysis** An uncontrolled prospective trial investigating the use of a 1550 nm fractionated erbium-doped fiber laser demonstrated that clinical AK count was reduced on average by 73% at 1 month, but this decreased to 66% at 3 months, and to 56% by 6 months [61].

In the uncontrolled prospective trial investigating the use of a 1540 nm Er:glass laser, reduction in AKs was scored on a scale of 0–4 (0: no improvement; 1: 1–25% reduction; 2: 26–50%; 3: 51–75%; 4: 76–100%). Following their first treatment, patients had a mean improvement of 2.4 on a scale of 0–4, and this increased to 2.9 following their second treatment, and up to 3.3 at 3 months after completing therapy [62].

**Harms** Ablative laser therapy may be associated with erythema, edema, infections, crust formation, pain, irritation, itching, hypopigmentation, acne, milia, and scarring [57,59,60]. Re-epithelialization usually occurs within 5–15 days after treatment, but may take longer for larger lesions. Most adverse effects are transient, but some such as dyschromia, atrophy/easy bruising, itching, and persistent crusting may last for over 6 months [60]. Both retrospective reviews reported occurrence of nonmelanoma skin cancers within treated fields in 8–12% of patients during follow-up of at least 1 year [59].

Fractional photothermolysis is associated with fewer adverse effects than ablative laser therapy, typically causing transient mild to moderate erythema, mild edema, superficial peeling, or superficial erosions without reports of scarring or postinflammatory hyperpigmentation in either study reviewed [61,62]. However, the prospective study of 14 patients treated with erbium-doped fiber laser found that, despite clinical improvement, 12/14 biopsies taken at 3 months posttreatment were positive for histologic features of AK and/or SCC [61].

**Comments** Ablative laser therapy appears to be highly effective in the immediate treatment of AK lesions. However, there are few studies with long-term follow-up, and those that have been done report variable recurrence rates. Side effects associated with this treatment may also produce long-term, undesirable cosmetic outcomes. In addition, laser therapy is a more expensive treatment in comparison with other treatment modalities such as 5-FU and cryosurgery. Further studies should be performed before Er:YAG or CO<sub>2</sub> laser therapy can become a routine treatment for AK. There are inadequate data to support fractional photothermolysis as monotherapy in the treatment of AK.

#### **Bowen's disease (strength of recommendation: B)**

The largest uncontrolled trial, a retrospective review, reported 44 patients with BD treated with CO<sub>2</sub> laser with 4 mm margins with a mean follow-up of 18 months [63]. A second uncontrolled trial reported the use of CO<sub>2</sub> laser therapy for BD on the legs [64]. This study treated 16 patients with 25 lesions with a 6-month follow-up. An update on patient health 12 months after discharge from this study was also published [65].

**Benefits** The larger study of 44 patients with BD treated with CO<sub>2</sub> laser showed a clearance rate of 98% overall, with a recurrence rate of 7% over a follow-up period between 8 and 52 months [63]. Only one treatment session was required for 86% of patients, while 11% of patients required more than one treatment session, with only one person not responding [63]. The study that treated BD on the legs found that eight of the 25 lesions took longer than 4 weeks to heal, but all lesions had healed completely at 8 weeks after treatment. Examination at 6 months found no recurrence of BD lesions, but at the 12-month follow-up there was a 12% recurrence of invasive SCC [64,65].

**Harms** Exudation, crusting, and erythema may follow laser treatment. Re-epithelialization occurs 7–10 days after treatment, but erythema may persist for 3 weeks or more. One Er:YAG laser study found no posttherapeutic dyspigmentation [66]. Secondary adverse effects occurred in 32% of patients, including minimal erythema and hypo- and hyperpigmentation, in one study, with only one patient acquiring a keloid [63]. Two of the 16 patients receiving CO<sub>2</sub> laser treatment on the legs developed infections requiring dressings and antibiotics [64]. No other adverse events were reported in this study; however, the study was published as an abstract in conference proceedings, and a detailed summary of all of the results was not provided.

**Comment** CO<sub>2</sub> lasers may be an alternate method for treating BD that allows for limited tissue injury resulting in better healing. However, if the tumor is deeper than expected, clearance rates may be inferior. Given that the progression to invasive malignancy was higher than expected (12%) in patients receiving laser treatment for BD on the legs [62], careful consideration should be given to the use of laser therapy until further studies are performed. Of note, there have been two small uncontrolled trials reporting the use of CO<sub>2</sub> laser therapy for BD on the digits, with either five or six patients, with a reported clearance rate of 100% within 10–24 days following the procedure [67,68]. However, recurrence rates differed between 0% at 84 months [68] and 20% at 5 months [67], likely due to difference in energy settings and margins. In these studies, CO<sub>2</sub> laser had no impairment of digital function. The suitability of CO<sub>2</sub> laser therapy for digital BD relates principally to two properties. First, CO<sub>2</sub> laser has the ability to vaporize the epidermis and the upper papillary dermis, leading to healing with minimal scar formation. This feature is desirable in mobile areas such as the fingers, where a contracting scar following excision may lead to functional impairment. Second, the concern that CO<sub>2</sub> lasers may not penetrate to a depth sufficient to eradicate perifollicular BD is obviated by the paucity of hair on the fingers. The risk of recurrence secondary to perifollicular involvement is therefore less of a concern in digital lesions than in lesions at other body sites. CO<sub>2</sub> lasers may thus be helpful for digital lesions, while other treatment options should be explored for lesions at other body sites until further studies are performed.

#### **Radiotherapy**

We found no systematic reviews or RCTs for either AK or BD.

#### **Actinic keratoses (strength of recommendation: C)**

We found only one case report using radiotherapy for AK [69].

**Benefit** One person with a large AK recalcitrant to 5-FU responded to fractionated radiotherapy [70].

**Comment** Given the absence of high-quality evidence for radiotherapy and the availability of other therapeutic modalities, radiotherapy should not be used for the treatment of AK.

#### **Bowen's disease (strength of recommendation: B)**

We found one retrospective study comparing the effect of radiotherapy with cryotherapy on lower leg lesions [55], as reported above. We also found two retrospective reviews, one of which contained 44 patients with BD treated with radiation therapy with a median follow-up of 2.6 years [71], and a smaller one with 11 patients with 16 BD lesions treated with radiotherapy [72].

**Benefits** Radiotherapy was more effective than cryotherapy in terms of recurrence (0% vs 6% at 2 years posttreatment) [55]. Skin cosmesis following radiotherapy is reported as "good" to "excellent" in the majority of patients in uncontrolled trials, with only 5–15% of irradiated skin considered "fair" to "unsatisfactory" [70,73]. In the study of 44 patients, orthovoltage X-rays were used, but there was no standard fractionation regimen. Complete remission occurred in 95% of patients, with a recurrence rate of 0.07% [71]. In this study, there was not a statistically significant association between the biologically effective dose and the recurrence rate [71]. All BD lesions followed in the retrospective study had 100% clearance at the time of last follow-up (the follow-up periods ranged from 17 to 1723 days) [72].

**Harms** The 100% clinical clearance and lack of recurrence using radiotherapy of leg lesions was offset by poor healing in 20% of lesions [55]. Poor healing in this study was defined as a residual ulcer requiring salvage surgery that ceased to show signs of continuing reduction in diameter, or was considered by the dermatologist to be progressing poorly over at least 3 months. In the larger retrospective study, the three BDs that were treated with higher radiation doses, all on extremities, resulted in Grade 4 toxicity, resulting in ulcers, one of which required amputation secondary to radiation necrosis [71]. The small retrospective study also reported poor healing, with 25% of lesions failing to heal due to ulcers, all of which were located on the lower leg [72]. Other reported adverse effects from uncontrolled studies included minor pain and burning during the procedure [74,75], short-term hypopigmentation [74], radiation dermatitis, and radionecrosis [75]. Poor healing, including radionecrosis, appears to be associated with older age, an irradiation field diameter >4 cm, and a total dose >3000 cGy [55,75].

**Comment** As noted by the authors of the retrospective comparative study of radiotherapy and cryotherapy, the conclusions must be considered in the light of the noncomparability of the groups. This study was retrospective, and shows a selection bias inasmuch as the severity and extent of a lesion often determines its initial therapy. A higher proportion of broad and thick lesions were thus treated in the radiotherapy group. Considering the radiotherapy group alone, however, may be informative in that poor healing was significantly related to age >90 years, a field irradiation diameter >4 cm, and a radiotherapy dose >3000 cGy. In view of the risk for poor healing, the authors suggested that patients meeting these criteria require cautious consideration in determining their candidacy for radiotherapy. However, in the larger retrospective study of 44 BDs treated with radiotherapy, there was no association between the biologically effective dose and recurrence, thus possibly allowing for effectiveness of lower doses with the prevention of treatment toxicity [71]. Caution should be used when selecting patients for

radiotherapy who have lesions in potentially poorly healing areas such as the lower legs, and moderate radiation treatment doses can result in a high rate of local control, reducing the potential for ulcer complications. Radiation therapy may be an option for larger lesions not amenable to other modalities in older patients.

#### **Chemical peels**

Chemical peels have only been investigated for AK.

#### **Actinic keratosis (strength of recommendation: A)**

We found no systematic reviews and one RCT. The RCT was a within-patient comparison of 5-FU combined with a glycolic acid (GA) peel versus the GA peel alone ( $n = 18$ ) [76]. We found two comparative studies [77,78] (with one follow-up study [79]) using trichloroacetic acid (TCA). Pretreatments included topical tretinoin (0.05%, increasing to 0.1%) in the first study [77] and Jessner's solution in the second study [78,79]. The concentrations of TCA varied from 35 to 40%.

The first study [77] was reportedly randomized. However, all of the patients pretreated with tretinoin had previously received topical therapies in addition to cryotherapy, whereas all of the patients without tretinoin pretreatment had previously received only cryotherapy. The study reported a 6-month follow-up. In the second study, a split-face design was used. One side of the face received a TCA chemical peel after pretreatment with Jessner's solution, and the other side received 5% topical 5-FU twice daily for 3 weeks. Despite a small sample size, follow-up was reported at 12 months [78] and 32 months [79].

**Benefits** Six months after eight weekly pulse peels, the combination of 5-FU and GA had cleared significantly more lesions than GA alone (92% vs 20%;  $P < 0.05$ ) [76]. No significant differences were observed for pretreatment with topical tretinoin before 40% TCA; AK was reduced by 20–75% in both groups. The authors used a reduction in the appearance of lesions, which was not necessarily a reduction in the number of lesions. Scores for photodamage decreased and telangiectasias improved with tretinoin pretreatment. Jessner's solution followed by TCA did not differ significantly from topical 5-FU: both yielded a 75% reduction in the number of lesions that persisted for 12 months. Analysis of eight patients at the 32-month follow-up showed that three (37%) had more lesions than at baseline, but that three patients maintained a 50% reduction from baseline.

The patients were extremely pleased with the cosmetic results of the TCA facial peels, and scored improvement significantly higher than the clinicians did. Patients preferred the facial peel to 5-FU because of the convenient single application and the shorter duration of adverse effects.

**Harms** Few side effects were associated with the combination GA peel and 5-FU or the GA peel alone. Slight facial erythema and mild xerosis were experienced, but resolved with an emollient cream [76]. The medium-depth facial peel procedures were associated with erythema lasting generally 10 days to 2 weeks. Mild desquamation was noted.

**Comments** The combination of 5-FU with a GA peel is more effective than a GA peel alone, which is likely too superficial to treat AKs. An RCT comparing 5-FU alone with 5-FU plus a GA peel would further elucidate what role, if any, GA has in the treatment of AK. Facial peel with TCA appears to be a viable option if the

patient is not a good candidate for cryotherapy (i.e., with widespread facial AK), or is intolerant to other topicals applied over the long term, such as 5-FU.

### Dermabrasion

Dermabrasion was investigated only for AK.

#### *Actinic keratosis (strength of recommendation: C)*

We found one unblinded comparative study [80] comparing recurrence rates for dermabrasion, 50% phenol chemical peels, and 1% topical 5-FU. Methodological problems included a small sample size, varying follow-up periods, lack of data on initial elimination rate, and lack of explicit evaluation criteria for remission or recurrence.

**Benefits** Dermabrasion yielded a longer time to recurrence than facial peel, but shorter times than 5-FU. However, no statistical data were presented [80].

**Harms** No information on adverse events was reported in the unblinded study. One case series of dermabrasion of the scalp [81] reported a conspicuous line marking the periphery of abrasion at postoperative weeks 6–8.

**Comments** This small study concluded that topical 5-FU was more effective and easier to use than dermabrasion. Although dermabrasion may produce longer term clearance than chemical peels, the case series [81] indicated a risk of scarring. Although larger studies are necessary for definitive conclusions to be reached, it would appear that the indication for dermabrasion as a primary therapeutic modality for AK is minimal.

### Surgery and electrodesiccation and curettage

Surgery is commonly used for BD, but not for AK.

#### *Bowen's disease (strength of recommendation: B)*

We found no systematic reviews or RCTs. We found one retrospective uncontrolled trial investigating surgical excision ( $n = 109$ ), as well as curettage and fulguration ( $n = 46$ ) and electrodesiccation ( $n = 16$ ) [82]. We found smaller retrospective uncontrolled trials for electrodesiccation and curettage (ED&C) ( $n = 20$  [83],  $n = 83$  [70],  $n = 52$  [84]). We found one prospective trial that compared cryotherapy ( $n = 36$ ) with ED&C ( $n = 44$ ) [54].

**Benefits** The 5-year recurrence rate, calculated by Kaplan–Meier curves, of surgical excision was 6% [82]. In this same study, the recurrence rate of curettage and fulguration was 7% based upon a mean follow-up duration of 28.7 months. There were no recurrences in electrodesiccation alone [82]. ED&C [70,83,84] resulted in complete clinical clearance rates ranging from 80 to 98%, with recurrences ranging from 2% up to 20% during a follow-up period of up to 18 years. Again, the time to recurrence was not reported. In the prospective study comparing cryotherapy with ED&C, there was a 100% clearance rate with a 9% recurrence rate over a 2-year follow-up period for ED&C, compared with a 36% recurrence rate for cryotherapy [54].

**Harms** No harms were reported with ED&C or with surgical excision, other than the understood risks of bleeding, infection,

scarring, and local anesthesia associated with minor surgery. ED&C compared with cryotherapy had superior healing, including decreased time to heal, with less pain and morbidity with ED&C [54].

**Comment** Surgical excision is commonly reported as the treatment of choice for BD, although no RCTs and only a few retrospective and one prospective series were found to support its use. The unmatched efficacy ascribed to surgical excision probably relates to the notion that excision of an in-situ neoplasm is, by definition, curative. The slow progression of BD to SCC suggests that additional outcomes such as healing, scarring, and patient preferences should be considered in determining the choice of treatment. The large series investigating ED&C suggested high efficacy, with tolerable recurrence rates during a sufficiently long follow-up period. ED&C may thus be a highly useful procedure for patients with small solitary lesions.

### What are the effects of topical therapy?

#### Topical retinoids

Topical retinoids were reported only for AK.

#### *Actinic keratoses (strength of recommendation: B)*

We found four double-blind RCTs investigating topical retinoids for AK [85–88]. The first study compared tretinoin cream ( $n = 25$ ) with Ro 14-9706 (arotinoid methyl sulfone cream;  $n = 25$ ) using a split-face design [85]. The second study was a parallel-group multicenter trial comparing 0.1% isotretinoin ( $n = 41$ ) with placebo ( $n = 47$ ) [86]. The third study was a four-arm comparison trial investigating the use of *all-trans*-retinoic acid cream, calcipotriol cream, a combination of the two creams, and a vehicle cream in renal transplant recipients [87]. Thirteen patients with multiple AKs applied each of the four treatments to different lesions, the order of which was randomly assigned. The fourth study compared the efficacy of 0.1% adapalene gel ( $n = 30$ ), 0.3% adapalene gel ( $n = 30$ ), and a vehicle gel ( $n = 30$ ) [88].

We also reviewed a large RCT comparing tretinoin versus vehicle cream in the prevention of keratinocyte cancers; response rates of AKs were reported as a secondary outcome ( $n = 1131$ ) [89].

**Benefit** Reductions in the number of AK lesions by 30% and 38% were reported for tretinoin and Ro 14-9706, respectively. Complete clearance of all lesions occurred in 8% of patients using tretinoin [85]. In comparison with placebo, 0.1% topical isotretinoin significantly reduced the number of facial lesions (65% vs 45%;  $P < 0.005$ ) [86]. No differences in the number of AK lesions were found between each of the four treatments used in the third study after 6 weeks of treatment [87]. It was concluded by the authors that neither *all-trans*-retinoic acid nor calcipotriol, nor a combination of these two creams, should be used to treat AKs in renal transplant recipients. After 9 months of treatment, patients treated with 0.3% adapalene gel had significantly fewer lesions in comparison with the baseline than those treated with vehicle cream ( $P < 0.05$ ) [88]. The complete lesion clearance rate for patients in both adapalene treatment groups was only 3%, while an increase in the numbers of lesions was observed in the vehicle group.

The RCT which examined the use of tretinoin 0.1% cream in the chemoprevention of keratinocyte cancers did not demonstrate any significant difference in AK counts between intervention and placebo [89].

**Harms** Severe local skin irritation was associated with topical tretinoin, whereas the irritation was mild to moderate with isotretinoin. No significant changes in laboratory parameters were observed. Higher levels of erythema, peeling, dryness, burning, and pruritus were associated with 0.3% and 0.1% adapalene treatment in comparison with the vehicle treatment [88].

The RCT comparing topical tretinoin with vehicle in the chemoprevention of BCC and SCC failed to show any significant difference in rates of nonmelanoma skin cancer: 53% of patients treated with tretinoin versus 54% of those treated with vehicle developed a BCC within 5 years, and 28% of the treated group developed an SCC compared with 31% of those treated with placebo. In addition, all-cause mortality was higher in the tretinoin group, although there is no clear causality between treatment and increased rates of patient death [89].

**Comments** Although some reduction in AK counts and size has been noted, few patients (8% [77] and 3% [88]) had complete clearance of lesions. In addition, tretinoin failed to prevent the development of nonmelanoma skin cancers [89]. The relatively high rate of reduction noted with placebo use indicates either that the study was flawed or that topical retinoids may not enhance the clearance of AK lesions sufficiently to be used as a standard treatment for AK.

### 5-Fluorouracil

Topical chemotherapy with 5-FU interferes with DNA and RNA synthesis. It is primarily used as a field treatment, for diffuse, ill-defined AK in which treatment of individual lesions is impractical or impossible. It is also used in BD.

#### *Actinic keratoses (strength of recommendation: A)*

We considered three systematic reviews [90–92]. There was significant overlap among the studies included in the systematic reviews.

**Benefits** The first systematic review combined 13 RCTs [57,93–104] to include in a meta-analysis [90]. The review included and compared studies which used either 0.5% or 5% 5-FU to treat lesions on the face, scalp, and extremities. Several measures of efficacy were assessed, including the average reduction in the mean number of lesions, the percentage of lesions cleared, as well as the number of patients with complete clearance at follow-up. Follow-up times for the included studies ranged from 4 weeks to 12 months. The combined data showed that treatment with 5% 5-FU resulted in an average reduction of 80% (59–100%) [57,93,94,97,100] in the mean number of lesions with 98% of lesions clear at 4 weeks [102] and 94% at 24 weeks [103] following treatment. Treatment with 0.5% 5-FU resulted in an average reduction of 86% (78–92%) in the mean number of lesions [95,104]. Across studies, an average of 49% (0–96%) of patients treated with 5% 5-FU and 35% (15–58%) of those treated with 0.5% 5-FU achieved total clearance [90].

The second systematic review combined six studies [78,95,104–107] to include in a meta-analysis [91]. The studies included used 0.5%, 1%, or 5% 5-FU as treatment, treated only the face and/or scalp, and measured the proportion of patients with no visible AKs at follow-up. The proportion of patients with complete clearance ranged from 0 to 100% (with treatment periods of 2–8 weeks and follow-up periods of 1–11 months). The pooled average for patient response was  $52.2 \pm 18\%$ .

The final systematic review combined nine studies [95,96,98,100,101,104,106–108] of 5-FU at either 5% or 0.5% concentration used on the face and/or scalp [92]. Efficacy was meas-

ured as complete clearance of all AKs at 4 weeks posttreatment for 0.5% 5-FU and 4–6 weeks posttreatment for the 5% 5-FU studies. Complete clearance rates with 0.5% 5-FU ranged from 15 to 58%, and those with 5% 5-FU from 43 to 100%. The single split-face study comparing 5% with 0.5% 5-FU had equivalent rates of complete clearance (43%) [100].

**Harms** 5-FU can be associated with pain, inflammation, and erosions. In the split-face study, twice-daily 5% 5-FU was found to cause more irritation, erosions, dryness, burning, pruritus, pain, and edema than once-daily 0.5% 5-FU [100].

**Comments** Although 5-FU has a high efficacy rate, one should note that it is associated with a high degree of morbidity, including pain, inflammation, and erosions, which may be intolerable to patients.

#### *Bowen's disease (strength of recommendation: A)*

We found no systematic reviews and two RCTs. One RCT was a comparison trial between 5% 5-FU and PDT [109], while the other was an RCT comparing MAL-PDT, cryotherapy, and 5-FU [53]. We found five uncontrolled trials addressing the therapeutic efficacy of 5-FU [82,110–113].

**Benefits** One year after treatment with either PDT or 5-FU, the complete clinical clearance rate of lesions in the 5-FU group was significantly less than in the PDT group (48% vs 88%;  $P = 0.006$ ) [109]. In the second RCT evaluated, the sustained complete response rate at 1 year of 5-FU was comparable to that of MAL-PDT ( $P = 0.19$ ); both were superior to cryotherapy ( $P = 0.047$ ). The clearance rate for 5-FU was 83% compared with 93% for PDT, but both superior to cryotherapy [53]. In the uncontrolled trials, clinical clearance rates were generally high, ranging from 85% [112] to 100% [83].

**Harms** Expected side effects include pain, pruritus, burning at the site of application, erythema, inflammation, widespread dermatitis reactions, and erosions [56,109,114]. In the nonrandomized studies, some authors suggest application of the medication four times daily to reduce the duration of treatment [110], while others advocate pulse therapy once or twice weekly to decrease the intensity of discomfort [115]. Although compliance with the latter regimen is higher, cure rates may be lower [116]. Lower-leg ulceration has been reported with 5% 5-FU cream [109,110], and an allergic reaction to 5-FU has been reported in conjunction with iontophoretic therapy [113].

**Comment** 5-FU appears to be of likely benefit in treating BD, although PDT maybe superior. As with AK, if patients are unable to tolerate the side effects of 5-FU, then we would expect the cure rate to drop off dramatically. For example, in the RCT, treatment was discontinued in five of the 33 lesions treated with 5-FU due to widespread dermatitic reactions (compared with none of 33 in the PDT group), which likely explains the low clearance rates for this treatment group (48%) [109].

The base in which 5-FU is delivered significantly affects its activity: 20% 5-FU in an ointment base, 5% 5-FU in a cream base, and 1% 5-FU in propylene glycol provide approximately equivalent cytotoxic activity [106,117–119]. Several studies investigated ways of enhancing 5-FU activity. Iontophoresis does not appear to improve 5-FU activity in comparison with 5-FU alone, but possibly could have the benefit of delivering 5-FU into adnexal structures



[70,83,112,113]. Application under occlusion, pretreatment with keratolytic agents, or deliberate exposure to sunlight (photosensitivity effect of 5-FU) are anecdotally reported as enhancement techniques [83]. The disparity in recurrence rates may relate to different therapeutic regimens: the recurrence rates were lower for studies that used 5-FU for longer than 4 weeks [83,112].

### Imiquimod

Imiquimod is an immunomodulator used as topical field treatment for AK. It is an agonist of toll-like receptor 7, which results in activation of both innate and adaptive immune responses [120,121]. It is available in two different concentrations (5% and 3.75%), and several regimens are used for treatment of AK.

#### *Actinic keratoses (strength of recommendation: A)*

We found three systematic reviews [91,122,123] with meta-analyses of RCTs [122,123] or RCTs and other relevant studies [91], which assessed the efficacy of 5% imiquimod in treating AK (Table 35.3). The first review [122] included five studies in its meta-analysis

[124–128], the second review [123] included four studies [124,125,127,128], and the third review [91] also included four studies [125,127–129]. We also reviewed six RCTs investigating the efficacy of alternate dosing schedules and concentrations of imiquimod [98,130–134].

**Benefit** A total of 1293 patients clinically or histologically diagnosed with AK were evaluated in the RCTs included in the first systematic review [122]. All of these studies sufficiently measured both the benefits and harms of imiquimod, but only one study [135] had a long enough follow-up period ( $\geq 1$  year) to effectively assess recurrence rates. Complete clinical clearance of all AK lesions occurred in 50% of patients treated with imiquimod, in comparison with only 5% in those treated with a vehicle cream [122]. The mean clinical response was not calculated in the second systematic review, which included 1266 patients [123], but complete clearance of lesions was more common in imiquimod-treated patients than in control-treated patients ( $P < 0.0001$ ). The third systematic review, which included a total of 393 patients, reported slightly higher

**Table 35.3** Summary of RCTs using imiquimod to treated AKs.

First author, ref	Intervention	Comparators	Study design	Study population	Sample size (n)	Outcome measures	Main results	Adverse effects	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Swanson (2010) [130]	2.5 and 3.75% imiquimod applied daily $\times 2$ , 2-week cycles	Placebo	RCT	AKs on face and scalp	479	Percentage of patients with complete clearance at 8 weeks	2.5% placebo 23.5% imiquimod 2.5% 26% imiquimod 3.75%	24–25% erythema 4–6% edema 1–6 % weeping/exudate 4–8% flaking/scaling/dryness 9–14% scabbing/crusting 9–11% erosions/ulceration	Adequate Adequate Adequate
Hanke (2010) [131]	2.5% and 3.75% imiquimod applied daily $\times 2$ , 3-week cycles	Placebo	RCT	AKs on face and scalp	490	Percentage of patients with complete clearance at 8 weeks	5.5% placebo 23% imiquimod 2.5% 34% imiquimod 3.75%	Pruritus, pain, influenza-like illness. 17% and 24% of imiquimod patients (2.5 and 3.75%) with adverse site reactions	Adequate Adequate Adequate
Gebauer (2009) [132]	5% imiquimod applied 2, 3, 5, or 7 times weekly $\times 8$ weeks	Placebo	RCT	AKs on forearms and hands	149	Percentage of patients with complete clearance at 8 weeks	0% placebo 3% 2 $\times$ /week 7% 3 $\times$ /week 3% 5 $\times$ /week 7% 7 $\times$ /week	59% itching 40% pain 15% burning 13–33% with severe grade adverse events	Adequate Not described Adequate
Serra-Guillen (2012) [133]	5% imiquimod cream applied TIW $\times 4$ weeks for 1 cycle	PDT and PDT followed by imiquimod	RCT	AKs on face and scalp	136	Percentage of patients with complete clearance at 4 weeks	27% imiquimod 10% PDT 37.5% PDT + imiquimod	50% mild local reactions 41% moderate local reactions 9% severe local reactions	Adequate Not adequate Not described
Jorizzo (2007) [134]	5% imiquimod, TIW $\times 4$ weeks for 1 or 2 cycles	Placebo	RCT	AKs on face and scalp	246	Percentage of patients with complete clearance at 4–8 weeks	27% imiquimod 1 cycle vs 4% placebo 54% imiquimod 2 cycles vs 15% placebo	16% with severe erythema, scabbing, crusting 2 patients with infection	Adequate Adequate Not described
Krawtchenko (2007) [98]	5% imiquimod TID $\times 4$ weeks for 1 or 2 cycles	Cryotherapy and 5-FU	RCT	AKs on head, neck or chest	75	Percentage of patients with complete clearance at 8 weeks	85% imiquimod 68% cryo 96% 5-FU	Not specified	Adequate Not adequate Not described

TID, three times a day; TIW, three times a week.

<sup>a</sup>Adequate if clear description of method of randomization and concealment of allocation of randomization.

<sup>b</sup>Adequate if assessors and participants were completely blinded to the study interventions.

<sup>c</sup>Adequate if an intention-to-treat analysis was carried out.

efficacy rates with imiquimod. The proportion of patients with complete clinical clearance for this review was  $71 \pm 12\%$  (mean plus/minus 95% CI) [122].

The RCTs reviewed (see Table 35.1) explored several different treatment regimens and demonstrated complete clearance rates of AKs on the head between 24 and 26% in patients treated with two cycles of 2.5% or 3.75% imiquimod daily for 2 weeks [130]. Efficacy increased to 34% complete clearance with two cycles of daily 3.75% imiquimod for 3 weeks [131]. AKs on the forearms and hands appear to be less responsive to treatment according to one study, which documented complete clearance rates of only 3–7% with 5% imiquimod applied for two, three, five, or seven times per week for 8 weeks, and did not to demonstrate a dose-dependent response [132]. The 5% imiquimod cream applied three times a week for a single 4-week cycle led to a 22–27% rate of complete clearance, while two 4-week cycles increased the percentage of patients cleared to 54–85% [98,133,134]. Histologic clearance was confirmed in 73% of lesions that demonstrated clinical resolution [98]. Of the patients that were clinically clear at 8 weeks following treatment, 73% remained clear at a 12-month check [98].

**Harms** Many local adverse events are associated with imiquimod treatment, including erythema, scabbing or crusting, flaking, erosion, edema, and weeping [122]. Use of imiquimod is also associated with influenza-like symptoms in up to 8% of patients [131,132]. Several studies noted that better clearance was observed in patients with the most severe adverse events [124,135]. Some authors also reported that the number of AK lesions increased in the initial stages of treatment [124–126]. It was proposed that this was more likely to be an appearance of subclinical lesions rather than formation of new lesions, and considered to be a benefit of imiquimod treatment.

**Comment** There is good evidence that imiquimod is an effective treatment for AKs on the face and scalp. Given the local adverse reaction that so commonly appears with imiquimod, we question whether the studies that were designed to be double blinded could have truly achieved blinding of the subjects who applied the cream. The FDA-approved guideline for use of imiquimod for treatment of AKs is twice weekly for 16 weeks. There appear to be multiple comparable dosing regimens that can be tailored to the needs and preferences of individual patients. Imiquimod treatment of AKs on the extremities appears to be less effective, and alternative treatments may be more appropriate in this area.

#### **Bowen's disease (strength of recommendation: A)**

We found a single, small RCT and two uncontrolled trials. The double-blinded RCT randomly assigned 31 patients to receive either a placebo cream ( $n = 16$ ) or imiquimod ( $n = 15$ ) daily for 16 weeks [136]. The largest retrospective review included 49 patients with BD treated with once-daily application of imiquimod for 6 weeks [137], while the other smaller uncontrolled trial treated 16 lesions of the lower limbs with once-daily application of imiquimod cream for 16 weeks [138].

**Benefits** The RCT reported that 73% of imiquimod-treated patients (once-daily application for 16 weeks) achieved complete resolution of BD lesions, which was significantly greater than in the placebo group, in which no resolution was achieved ( $P < 0.001$ ), with a follow-up period of 28 weeks [136]. In the larger retrospective review with 49 patients, there was an 86% clinical clearance rate

over a mean follow-up of 19 months in patients using imiquimod (once-daily application over mean of 9 weeks). In 10% of the patients who failed therapy, they had no discernible inflammatory reaction [137]. The second uncontrolled study reported a 93% treatment response (15 of 16 patients), evidenced by no residual tumor on histology, over a mean follow-up time of 6 months [138]. Although six patients withdrew prematurely because of local skin reactions and were not included in the final analysis, an ITT analysis showed that 88% (14 of 16 patients) had no residual tumor [138].

**Harms** In the RCT, imiquimod treatment was generally well tolerated, and no serious adverse events were reported [136]. Two imiquimod-treated patients withdrew from the study, one due to infection at the treatment site and the other due to an inflammatory reaction. This reaction was presumed to have been due to treatment application to an area greater than the original lesion. No recurrence of lesions was reported during the 9-month follow-up period. In uncontrolled BD trials, adverse events included marked local skin irritation requiring discontinuation of therapy, superinfection requiring antibiotics, and satellite lesions in adjacent sun-damaged areas [137,138].

**Comments** Imiquimod 5% cream appears to be an efficacious treatment for BD. Imiquimod 5% can be considered an alternative to surgery, either if the patient refuses surgical treatment or if the tumor's size or location makes surgical resection challenging. It can be used in lower limbs, particularly for large lesions on the lower extremity, such as the shin, where poor healing is of particular concern. Of note, if a patient does not respond to imiquimod with an inflammatory reaction, the medication should be stopped and alternative therapy should be chosen. There have been reports of invasive SCC and eruptive keratoacanthomatous carcinomas arising after imiquimod therapy for BD [139,140]. The dosing schedule and length of treatment require further evaluation in RCTs, as well as longer follow-up time.

#### **Ingenol mebutate**

Ingenol mebutate is a topical therapy recently approved for treatment of AK. It is a macrocyclic diterpene ester, derived from the sap of the plant *Euphorbia peplus*. Its effect is mediated through multiple pathways, including both rapid and direct keratinocyte cell death as well as by specific immune response via activation of protein kinase C delta and neutrophil-mediated oxidative burst [141–143]. It is provided in two concentrations, one for the face and scalp (0.015%, applied for three consecutive days) and one for the body and extremities (0.05%, applied for two consecutive days).

#### **Actinic keratoses (strength of recommendation: A)**

We identified three RCTs evaluating the use of ingenol mebutate in the treatment of AKs. The first RCT is a phase IIa study ( $n = 58$ ) that compared vehicle alone with the use of three different concentrations of ingenol mebutate gel (0.025%, 0.01%, and 0.05%) and two different treatment schedules: arm A treated on days 1 and 2, and arm B treated on days 1 and 8. Each patient had a representative lesion biopsied prior to, and following, treatment to evaluate for histologic clearance [144]. The second RCT that we reviewed was a multicenter, dose-finding study ( $n = 220$ ) [145]. This study also compared several different treatment protocols with vehicle alone: ingenol mebutate 0.025% gel for three consecutive days, 0.05% gel for two consecutive days, and 0.05% gel for three consecutive days. Patients were assessed at day 57 for clinical clearance of AKs.

The final RCT we reviewed was also a multicenter study comparing the use of vehicle alone with treatment ( $n = 547$ ) [146]: 269 patients applied ingenol mebutate 0.015% gel to a 25 cm<sup>2</sup> contiguous field on the scalp and/or face for three consecutive days and 222 patients applied ingenol mebutate 0.05% gel to a 25 cm<sup>2</sup> contiguous field on the body or extremities for two consecutive days. Clinical clearance was evaluated at 57 days. This study also completed an observational period of 12 months and documented recurrence/new lesions in previously treated fields.

**Benefits** In the RCT that examined the use of three different concentrations of ingenol mebutate on two different dosing schedules, it was shown that there was no statistically significant difference between treating on consecutive days (days 1 and 2) versus treating on days 1 and 8. The 0.05% gel was found to be the most effective, with 53 of 75 treated lesions clinically cleared at day 85 and 67% of patients with 80% or greater complete clinical lesion clearance [144].

In the second RCT reviewed, the best results at day 57 were seen with the 3-day course of 0.05% ingenol mebutate gel, with 54% of patients showing complete clearance and resolution of 60% of lesions documented prior to treatment. A 2-day course of 0.05% ingenol mebutate gel resulted in complete clearance rates of 44% and clearance of 44% of baseline lesions [145].

For the final RCT, patients who treated face and/or scalp with a 3-day course of 0.015% ingenol mebutate gel had a complete clearance rate of 42% and a median reduction in number of lesions of 83% at day 57. Treatment of trunk and extremities resulted in a complete clearance rate of 34% and a median percentage reduction in lesions from baseline of 75% at day 57. Observational 12-month follow-up of 146 patients with complete clearance at day 57 demonstrated that a mean of 85–87% of lesions in the treatment area at baseline were still clear at 12 months (torso and extremities vs face and scalp), but 50–53% of patients had developed one or more new lesions within the treatment area [146].

**Harms** The most commonly reported adverse effects were local site reactions such as erythema, flaking/scaling/dryness, and scabbing/crusting; these reactions were found to be most intense on day 3 to day 8; 98% of patients reported erythema on treatment day 3 [144,145]. The mean maximum composite local-skin-response score for both scalp/face and body/extremities on a scale of 0–24 was  $9.1 \pm 4.1$  versus  $1.8 \pm 1.6$  for placebo, and 98% of patients using ingenol mebutate reported local skin-response scores above baseline. Other common side effects included pain, pruritus, and irritation [146].

**Comments** Overall treatment with ingenol mebutate appears to be well tolerated with the additional benefit of a shorter treatment course than other patient-applied topical therapies.

The phase II RCT that evaluated lesions for histologic clearance at day 85 did not demonstrate a statistically significant difference between AKs treated with ingenol mebutate and those treated with vehicle only. Of lesions treated with vehicle, 42% demonstrated histologic clearance on day 85, suggesting that the initial biopsy may have had some effect upon the resolution of the lesion [144].

## Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug formulated as a 3% topical gel in 2.5% hyaluronate sodium.

### Actinic keratosis (strength of recommendation: A)

We found one systematic review [147], and one phase IV, single-arm, open-label, 1-year extension study [148]. The systematic review conducted a meta-analysis of three RCTs ( $n = 364$ ) [149–151] and compared the results 30 days following 60 days of therapy with twice-daily diclofenac versus placebo gel [147]. The extension study examined patients 1 year after completing 90 days of treatment with twice-daily diclofenac, and examined the number of patients with 75% clearance or greater of their baseline AK lesion numbers ( $n = 76$ ) [148].

**Benefits** The meta-analysis of the three RCTs investigated in the systematic review [147] revealed that 40% of patients experienced complete lesion clearance at 30 days after the end of treatment, in comparison with 12% of patients treated with a placebo gel [147]. Complete lesion clearance rates (for two separate trials) 30 days after a 90-day treatment with diclofenac were 47% and 34%, in comparison with 19% and 18% for the placebo groups [152].

The phase IV, one-year extension study found that 91% of patients maintained clearance of at least 75% of their baseline lesions at 1-year follow-up, and 70% of patients had 75% or greater clearance of total cumulative lesions (baseline lesions plus any new AK lesions).

**Harms** The most common adverse effects reported after treatment with 3% diclofenac in 2.5% hyaluronic acid gel are pruritus, contact dermatitis, dry skin, rash, and scaling. Treatment is generally well tolerated [147].

**Comments** Treatment of AK using 3% diclofenac in 2.5% hyaluronic gel appears to be well tolerated, but with lower efficacy than other topical treatments reviewed. The lesion clearance rates in all of these studies were clinically assessed only, which may lead to overestimation. However, limited follow-up at 1 year does suggest that response is maintained following clinical clearance of lesions in the majority of patients.

### Bowen's disease (strength of recommendation: C)

We found no systematic reviews, RCTs, or case series that included more than 10 lesions. We found one case series, which treated two patients (each with one BD lesion) with 3% diclofenac in 2.5% hyaluronic gel twice daily for 90 days [153].

**Benefits** Both patients were clinically free of BD 10–12 months after treatment.

**Harms** One patient developed severe dermatitis and had to discontinue treatment after 80 days.

**Comments** Insufficient research has been conducted to establish the efficacy of this treatment for BD lesions. Given the high rates of SCC transformation of BD, and the low response rate of AK to diclofenac, it seems questionable and unethical for any further research to be conducted.

### Photodynamic therapy

PDT involves application of a topical photosensitizer, usually a porphyrin derivative, followed by activation by visible light. Visible light activates the photosensitizer in the presence of oxygen, creating reactive oxygen species, which selectively destroy the target

tissue. The two most commonly used photosensitizers are topical aminolevulinic acid (ALA) and MAL.

#### **Actinic keratoses (strength of recommendation: A)**

Although multiple reviews have been published on the use of PDT in AK, none of them includes a meta-analysis of the available data. Owing to the large number of RCTs examining the use of PDT in treatment of AK, we elected to review only those trials that contained at least 100 subjects. We examined 11 RCTs exploring the use of MAL- or ALA-PDT with activation by several different light sources (Table 35.4) [42–45,154–160].

**Benefits** Six RCTs investigating the use of MAL-PDT with a red light source found that 59–68% of patients experienced complete clearance of their AKs 3 months following treatment [154,155,159], and that 69–91% of individual lesions were cleared at 3 months [42–44,154,155,159] and 78–87% of lesions at 6 months [42,45]. Activation of MAL by 1.5 or 2.5 h of daylight resulted in clearance of 68% of AK at 3 months [156].

The percentage of patients with complete clearance at 3 months following ALA-PDT with red light activation was found to be 62–78% [157–159], and the percentage of AK with complete clearance at 3 months was 82–90% [158,159]. Activation of ALA by blue light resulted in 73% of patients with complete clearance at 3 months with 91% of individual AKs showing complete clearance [160].

Cosmetic outcomes with PDT were also measured in several of the RCTs reviewed [43–45,157,159], with 43–96% reporting “good” to “excellent” cosmetic results with ALA- and MAL-PDT.

**Harms** PDT is associated with a stinging or burning sensation during photoirradiation, as well as postprocedural erythema, edema, blistering, crusting, and other “phototoxic reactions” [42–45,154,155,157–160].

**Comments** PDT, using either ALA or MAL as a photosensitizing agent, has been highly successful in treating AK lesions, especially if they are widespread. Although the healing process is somewhat lengthy, it is comparable to the events experienced by patients following 5-FU and other topical regimens. It is an expensive treatment that requires a trained specialist and costly equipment to administer it and requires long office visits to complete. Despite this, several studies have reported patient preference for PDT over other topical treatments for AK [42–44].

#### **Bowen's disease (strength of recommendation: A)**

We found no systematic reviews, three RCTs, and several unblinded controlled trials. One RCT compared PDT using the photosensitizing agent MAL ( $n = 96$ ) with placebo-PDT ( $n = 17$ ), or with another standard therapy [53]. The standard therapy involved either cryotherapy or fluorouracil, as chosen by the treating investigator. The second RCT investigated 61 lower leg lesions to compare the efficacy of green light and red light wavelengths after incubation with 20% 5-ALA for 4 h [161]. The third RCT compared PDT using aminolevulinic acid ( $n = 20$ ) with 5% 5-FU ( $n = 20$ ) [109]. Compared with other treatment modalities for BD, there have been several prospective and retrospective trials, with greater than 50 patients, evaluating the use of ALA-PDT [162–165].

**Benefits** The complete response rate 3 months after treatment for lesions treated with MAL-PDT with red light was 93% in compari-

son with 21% for placebo-PDT-treated lesions [53]. At 12 months, the sustained clinical response for MAL-PDT was 80%, with a statistically significant difference between MAL-PDT and the combined standard therapy group ( $P = 0.04$ ). The recurrence rates for these treatments (1 year after treatment) were 15% for MAL-PDT and 50% for placebo-PDT [53]. Ninety-four percent of patients who experience pain related to MAL-PDT reported that it was of mild or moderate severity. Comparing red versus green light in ALA-PDT, lesions receiving red light showed a significantly greater clinical clearance rate, as determined by the dermatologist's examination (94% vs 76%;  $P < 0.002$ ), as well as a lower recurrence rate (6% vs 38%) in comparison with green light (odds ratio 0.13; 95% CI, 0.04–0.48) [161]. The authors attribute this difference to the reduced depth of tissue penetration by green light, postulating that peri-appendageal BDs (which may extend up to 3 mm in depth) may survive ALA-PDT using less-penetrating wavelengths. No ulceration, infection, scarring, or photosensitivity reactions were reported in either group. There was no significant difference in pain between the groups, and the majority of patients reported “none” to “moderate” pain [161]. In the third RCT, complete clearance 6 weeks after treatment was reported in 88% of lesions treated with ALA-PDT, in comparison with 67% in lesions treated with 5-FU [109]. After 12 months of follow-up, lesion recurrences reduced these rates to 82% for PDT and 48% for 5-FU (odds ratio 4.78; 95% CI, 1.56–14.62).

In the uncontrolled trials, including only studies with greater than 50 patients, evaluating the use of ALA-PDT, the clearance rates range from 84 to 96%, with recurrence rates ranging from 11 to 31% [162–165].

**Harms** Adverse effects of PDT include treatment-induced pain, requiring anesthesia, in up to 25% of lesions [166–168], skin fragility and dyspigmentation [168–170], permanent hair loss [170], toxic reactions to ALA cream [167], and photosensitivity reactions [166].

**Comments** PDT appears promising for the treatment of BD. While the first RCT was double blinded [49], investigators in the second RCT were not blinded to the type of light used [161], thus potentially introducing bias. Blinding was impossible in the third RCT [109] owing to the differences in treatment types being compared in the study. Although more objective outcomes, such as clinical clearance and recurrence, are less susceptible to bias related to lack of blinding, the validity of the results concerning treatment-related pain may be improved with blinding. The analyses for the first [53] and second RCTs [161] were not based on an ITT approach, since patients who discontinued treatment or were lost to follow-up were excluded from the final analysis – thus risking overestimation of the efficacy of the treatment and underestimation of recurrences. PDT can be considered an alternative nonsurgical treatment option for BD, especially when there are a large number of lesions.

### **What are the effects of intralesional or oral medication?**

#### **Oral retinoids**

#### **Actinic keratoses (strength of recommendation: B)**

We identified two RCTs investigating the use of etretinate in treatment of AKs, as well as one RCT examining the efficacy of acitretin in immunocompetent hosts in reducing the rates of nonmelanoma skin cancer, which reported reduction in AK as an additional



Table 35.4 Summary of RCTs of photodynamic therapy for AK.

First author, ref	Intervention	Comparators	Study design	Study population	Sample size (n)	Outcome measures	Main results	Adverse effects	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Pariser (2008) [154]	MAL-PDT, red light	Placebo-PDT	RCT	Multiple AKs on face/scalp	100	Percentage of lesions with complete response at 3 months Percentage of patients with complete clearance at 3 months	MAL 86% vs placebo 52%  MAL 59% vs placebo 15%	Erythema 77% Burning sensation 72% Pain 60% Edema 28% Scab 26% Skin discomfort 23% Blister 15% Skin exfoliation 11%	Adequate Adequate Adequate
Szeimies (2009) [155]	MAL-PDT, red light	Placebo-PDT	RCT	AKs on face and scalp	115	Percentage of lesions with complete response at 3 months Percentage of patients with complete clearance at 3 months	MAL 83% vs placebo 29%  MAL 68% vs placebo 7%	Pain 55% Erythema 52% Burning sensation 36%	Adequate Adequate Adequate
Freeman (2003) [43]	MAL-PDT, red light	Placebo-PDT Cryotherapy	RCT	AKs on face/scalp	204	Percentage of lesions with complete response at 3 months	MAL 91% vs cryo 68% vs placebo 30%	Burning 46% Erythema 24% Edema 8.5% Skin peeling 6% Skin bleeding 5% Blisters 3% Itching 5% Crusting 2%	Adequate Not adequate Adequate
Szeimies (2002) [44]	MAL-PDT, red light	Cryotherapy	RCT	AKs on face/scalp/other, unspecified locations	202	Percentage of lesions with complete response at 3 months	MAL 69% vs cryo 75%	43% with local adverse events Burning 32% Pain 10% Crusting 5%	Adequate Not adequate Not described
Morton (2006) [42]	MAL-PDT, red light	Cryotherapy	RCT	AKs on face/scalp	119	Percentage of lesions with complete response at 3 months 6 months	MAL 84% vs cryo 75% MAL 87% vs cryo 84%	62% with "phototoxic reaction"	Adequate Not adequate Adequate
Kaufmann (2008) [45]	MAL-PDT, red light	Cryotherapy	RCT	AKs on the face/scalp	121	Percentage of lesions with complete response at 6 months	MAL 78% vs cryo 88%	45% with "photosensitivity reaction"	Adequate Not adequate Adequate
Wiegell (2012) [156]	MAL-PDT, daylight 1.5 h	MAL-PDT, daylight 2.5 h	RCT	Multiple AKs on face/scalp	145	Percentage of lesions with complete response at 3 months	Combined data 68% (no significant difference between groups)	Not addressed	Adequate Not adequate Adequate

Continued

Table 35.4 Continued

First author, ref	Intervention	Comparators	Study design	Study population	Sample size (n)	Outcome measures	Main results	Adverse effects	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Szeimies (2010) [157]	ALA-PDT, red light	Placebo-PDT		Multiple AKs on face/scalp	122	Percentage of lesions with complete response at 3 months	ALA 81% vs placebo 22%	Burning, itching, edema, induration	Adequate Adequate Not adequate
Hauschild (2009) [158]	ALA-patch PDT, red light	Placebo-PDT Cryotherapy	RCT	AKs on face and scalp	498	Percentage of patients with complete clearance at 3 months	ALA 64% vs placebo 11%		
						Percentage of lesions with complete response at 3 months	ALA 82–89% vs cryo 77% vs placebo 19–29%	Erythema 94–97% Irritation 85–88% Pain 35–43%	Adequate Not adequate Adequate
						Percentage of patients with complete clearance at 3 months	ALA 62–67% vs cryo 52% vs placebo 6–12%	Pruritus 6–15% Vesicles 4–5% Scab 10–17% Exfoliation 11–20% Erosion 3% Infection 1%	
Dirschka (2012) [159]	ALA-PDT, red light	MAL-PDT, red light Placebo-PDT	RCT	Multiple AKs on face/scalp	571	Percentage of lesions with complete response at 3 months	ALA 90% vs MAL 83% vs placebo 37%	Erythema, edema, exfoliation, induration, scabbing, vesiculation, pruritus	Adequate Adequate Adequate
						Percentage patients with complete clearance at 3 months	ALA 78% vs MAL 64% vs placebo 20%		
Piacquadio (2004) [160]	ALA-PDT, blue light	Placebo-PDT	RCT	AKs on face/scalp	243	Percentage of lesions with complete response at 3 months	ALA 91% vs placebo 25%	Discomfort 90% Erythema 99% Edema 38% Crusting 49% Pruritus 30% Scaling 31% Pigmentary changes 5%	Adequate Not adequate Not adequate
						Percentage of patients with complete response at 3 months	ALA 73% vs placebo 8%		

<sup>a</sup> Adequate if clear description of method of randomization and concealment of allocation of randomization.<sup>b</sup> Adequate if assessors and participants were completely blinded to the study interventions.<sup>c</sup> Adequate if an intention-to-treat analysis was carried out.

outcome [171–173]. The two studies with etretinate used a crossover design and followed patients from 2 to 18 months. The acitretin study followed patients for 2 years while administering either placebo or acitretin 5 days per week.

**Benefits** Both RCTs for etretinate did not report the relevant outcomes, but instead recorded lesion size, the usefulness of which is dubious. Oral etretinate (Tegison) reduced the lesion size in 82–86% of patients, with improved overall grading of lesions in 89–100% of patients. Placebo resulted in lesion size reduction in only 4% of patients, with 17% of patients with improved overall grade following treatment [172,173].

Treatment with acitretin was not found to result in any significant difference in the number of AKs between those patients on active treatment and those receiving placebo [171].

**Harms** Dry lips and mouth may occur in a high proportion of patients using etretinate, although symptoms are alleviated with dose reduction. Mucocutaneous xerosis and alopecia were more frequent in patients receiving acitretin, as was hypertriglyceridemia [171]. Transient elevations of serum cholesterol and triglycerides, as well as one case of drug-related hepatitis, were reported with etretinate [173].

**Comments** The rates of reduction in lesion size and grading appear to be significantly better for etretinate than placebo. However, these results are based on outcome measurements that are limited in their usefulness. One should also be careful of crossover study designs, in which a considerable carry-over effect is likely. If insufficient time is allowed for the etretinate to wash out in the patients in whom etretinate was given before the placebo, then the effects of etretinate were probably confounding the results of the placebo.

While there is literature supporting the use of acitretin in treatment and prevention of AK in the solid organ transplant population, it is unclear if this evidence can be extrapolated to immunocompetent patients [174,175]. The data available to date do not support the use of systemic retinoids in the treatment or prevention of AKs in this group.

#### **Bowen's disease (strength of recommendation: C)**

We found no systematic reviews, RCT, or uncontrolled trials involving 10 or more subjects. Interestingly, there have been a few small uncontrolled case series investigating the use of acitretin or etretinate in treatment of BD in patients with chronic arsenicism [176–178].

**Comment** Oral retinoids cannot be recommended for treatment of BD, given that in some studies residual tumor cells were found in patients.

#### **Capecitabine**

##### **Actinic keratoses (strength of recommendation: B)**

Capecitabine is a prodrug of 5-FU and is the first oral chemotherapeutic agent approved by the FDA. It is used to treat primary and metastatic colon cancer as well as metastatic breast cancer. Inflammation and resolution of AKs have been reported in individual patients during treatment with capecitabine [179–181]. There are no RCTs examining the use of capecitabine in treatment of AKs, and only two small observational studies in the solid organ transplant population [182,183].

**Comment** At this time there is insufficient evidence available to recommend treatment with capecitabine for AK in immunocompetent patients.

#### **Bowen's disease (strength of recommendation: C)**

There are no studies or reports documenting the use of capecitabine in the treatment of BD.

#### **Interferon**

##### **Actinic keratoses (strength of recommendation: B)**

We found one double-blind, placebo-controlled, parallel-group RCT each for intralesional interferon alpha [184] and topical interferon gel (Intron A; interferon alpha-2b) [185]. The studies included 16–23 patients, with a posttreatment follow-up period of 1–2 months. No indication of complete cure on a per-patient basis was indicated.

**Benefit** High-dose interferon given intralesionally three times weekly for 2–3 weeks produced complete cure in 47–93% of the lesions treated [184]. No complete cures were produced with topical interferon gel, and only 9% of the lesions ( $n = 35$ ) showed marked improvement ( $>75\%$ ) [185].

**Comment** While high doses of intralesional interferon appear promising, it is impractical in the clinical setting and it is unlikely that the topical formulation will be of much benefit. However, intralesional interferon could be reserved for those patients who cannot use more conventional and economical therapies. In addition, adverse reactions, including myalgia, fever, and headaches, are common.

#### **Bowen's disease (strength of recommendation: C)**

We found one small unblinded quasi-RCT comparing topical 5-FU (5% cream) with intralesional interferon alpha-2b (1 000 000 units/injection) in the treatment of BD and AK [107]. We found one case report of one patient with multiple BD and AKs treated with oral isotretinoin at 1 mg/kg per day and interferon alpha-2a given subcutaneously  $3 \times 10^6$  U three times per week [186].

**Benefit** In the small trial, the 5-FU group showed 100% clinical clearance, whereas the interferon group showed 90% clinical clearance at the 8-week assessment. However, the study did not differentiate between BD and AK [107]. In the case report, although the patient had clinical improvement of her lesions, further treatment was required [186].

**Comment** Intralesional interferon may be a good option for BD in those not responsive to more conventional and economical therapies. Systemic interferon use has not been studied, and side effects are common with flu-like symptoms.

#### **Bleomycin**

There is one anecdotal report of the successful use of intralesional bleomycin in the treatment of BD [187].

#### **What are the effects of application of sunscreen?**

##### **Actinic keratoses (strength of recommendation: A)**

Given the pathophysiology of the development of AKs and BD is related to UV exposure, the use of topical photoprotection in preventing the development of nonmelanoma skin cancers has been

studied. We found three randomized control trials evaluating the use of routine sunscreen in the prevention of AKs [188–190]. There have been nonrandomized control trials in the transplant population showing the use of sunscreen (sun protection factor (SPF) >50, high-UVA) also reduces the development of AK, as well as non-melanoma skin cancers [191].

### Benefit

In an Australian study of 588 patients, those who used daily broad-spectrum UVA–UVB of SPF 17, applying 1.5 ml to the head/neck as well as 1.5 ml to each forearm/hand, over a 7-month period had a fewer number of new AKs compared with the placebo group (difference, 0.7; 95% CI, 0.2–1.3) with an 81% compliance rate [188]. The Nambour Skin Prevention Trial evaluated the use of daily SPF 15 plus sunscreen and oral betacarotene 30 mg supplementation in an Australian population of 1621 study participants over 4.5 years in the prevention of AKs, as well as nonmelanoma skin cancer [190,192]. In the daily sunscreen group in the first 2 years of the study, there was a 20% increase in solar keratosis compared with a 57% increase in solar keratosis in the placebo group ( $P < 0.05$ ) [190]. For the last 2 years of the study, the difference was not significant. The use of daily SPF 29 in a Texas population had a 36% reduction ( $P$ -value 0.001) in annual AKs over patients who were in the placebo group over a 2-year period (total study population of 50 people) [189]. In this study, the effect was greatest for lighter skinned individuals with more AKs at baseline, which are patients at higher risk for developing AKs.

### Harm

The most common side effects was burning of product, especially when coming in contact with eyes [189]. Other side effects included acneiform eruptions. There was no mention of allergic or irritant contact dermatitis in these studies.

### Comment

The use of sunscreens has been shown to decrease the development of AK. However, sunscreen use needs to be on a daily basis to have such effects. There have been reports of allergic and irritant reactions to UV filters contained in sunscreens. Given that vitamin D is formed within the skin through the action of UV radiation, monitoring of vitamin D status is important in patients who strictly avoid the sun and are diligent about wearing sunscreen. In both immunocompetent and immunosuppressed patients, the use of sunscreens with broad-spectrum UVA and UVB protection is recommended, in combination with the use of photoprotective clothing, such as wide-brimmed hats. Given that many withdrawals from the study were due to either misconception that the sunscreen was working or the dislike of the sunscreen, education and choosing a product that patients will use daily is essential.

### Implications for clinical practice: spontaneous regression rates and future studies

As discussed in the “Background” section, the prognosis for patients with AKs without treatment is confounded by the spontaneous regression rate. A study in Queensland reported a spontaneous regression rate of 85% (95% CI, 75–96%) in people with prevalent AK (AK diagnosed on a person during their first examination) and 84% (95% CI, 72–96%) in persons with incident AK (AK appearing for the first time during the study) [31]. Such spontaneous regression rates emphasize the need for a comparison arm in order for the study to be well designed. Moreover, while most studies utilize the disappearance of AKs as the endpoint of the study, the more relevant clinical outcome is to determine whether the therapy in question really reduces the risk of SCC in the long term.

## Key points

### Actinic keratoses

- We found good evidence to suggest that cryotherapy, PDT, topical 5-FU, ingenol mebutate, and imiquimod may be beneficial in the treatment of AK.
- Fractional photothermolysis, radiotherapy, and topical retinoids are not appropriate treatments for AK.
- Different modalities of treatment may be preferred in spot treatment of discrete lesions versus field treatment for diffuse disease.
- The evidence supporting the efficacy of most therapies is insufficient or limited.
- It is still unclear whether any of the treatments reduce the incidence of invasive SCC – the outcome of most importance.
- Studies were not consistent in choosing their units of analysis. Some used the number of lesions, others used persons cleared, and others used both as their units of analysis. Readers should determine which unit is most relevant to their practice.
- The use of daily broad-spectrum sunscreen with photoprotective clothing should be encouraged in all patients because it reduces the development of AKs.
- Given the high rate of spontaneous resolution of AKs over time, debate still exists on whether all patients need treatment.

### Bowen's disease

- The evidence for treatment of BD is generally of poor quality, with few RCTs.
- The choice of therapy in BD should take into account the location of the lesions, particularly the lower legs and the digits, where healing may be complicated.
- ED&C, PDT, and cryotherapy are acceptable first-line treatments for BD, given the available evidence.
- ED&C may be superior to cryotherapy for lower leg lesions.
- Radiotherapy might be an option for larger lesions where other therapies are not an option.
- The topical therapies 5-FU and imiquimod have shown efficacy but might have poorer outcomes compared with surgical approaches.
- There is no evidence to support the use of topical diclofenac in the treatment of BD.
- There have been no studies on the use of dermabrasion, topical retinoids, or topical ingenol mebutate in the treatment of BD.
- There appears to be good evidence for the superior efficacy of red light over green light in PDT with ALA.



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## Other useful resources

For further information on the treatment of AK or BD, the British Association of Dermatologists publications on the management of BD [193] and AK [194] may also be helpful.

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# Kaposi sarcoma

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## Background

In 1872, Moritz Kaposi, a Viennese dermatologist, first-described Kaposi sarcoma (KS) as an “idiopathic multiple pigmented sarcoma of the skin.” [1] For more than a century the disease existed as a relatively obscure condition, affecting chiefly the legs of older men of eastern European, Mediterranean, and/or Jewish descent.

In 1981, KS “re-emerged” as a disease of increased incidence and importance, occurring in association with acquired immunodeficiency syndrome (AIDS) [2]. Another major advance in the subject occurred in 1994, when human herpesvirus 8 (HHV8) was implicated in the etiology of the disorder [3]. To date, HHV8 infection has been demonstrated in essentially all forms of KS (whether “AIDS related” or not), and it is believed this infection is requisite to development of disease, although a permissive environment of immunosuppression is also likely involved.

Four clinical variants of KS are widely recognized:

- **Classic KS.** This affects chiefly older men of Mediterranean or Jewish heritage, with peak incidence after the sixth decade. Classic KS presents as purple–blue plaques upon the lower legs (Figure 36.1). The disease is often largely indolent, but it may progress over years. Morbidity in classic KS is typically limited, but it may include also venous stasis and chronic lymphedema. Mortality is truly exceptional. It has been reported that up to a third of patients with classic KS may develop a second malignancy; in particular, non-Hodgkin lymphoma [4].
- **Epidemic (AIDS-related) KS.** This is the most common form of KS in the USA, and in the developed world. In fact, early in the HIV/AIDS epidemic, it was thought that KS (Figures 36.2 and 36.3) occurred up to 20 000- to 50 000-fold more often among AIDS patients than the general population [5,6]. Epidemic (AIDS-related) KS is often more aggressive than most other forms of the disease, and patients may present with extensive disease. KS remains an AIDS-defining illness. The presence of decreased CD4 counts is the most important prognostic factor in the development of epidemic (AIDS-related) KS, and in some series less than 10% of HIV-infected patients who develop KS have a CD4 count  $>500/\mu\text{L}$  [7]. However, in a small number of patients even persistent KS may present in the absence of relatively higher CD4 counts [8]. Decades ago, oral KS was the first

recognized clinical manifestation of AIDS in about 25% of patients, whereas today, with widespread use of highly active antiretroviral therapy (HAART), KS is seen relatively infrequently in AIDS patients (2–3% of patients).

- **Endemic (African) KS.** This occurs in sub-Saharan Africa, mostly affecting HIV-negative women and children (Figure 36.4). Endemic (African) KS may follow an indolent or aggressive course. In general, endemic (African) KS affects lymph nodes more often than classic KS, but other etiologic factors, beyond HHV8 infection, are not well understood. Some investigators have implicated a reduced wearing of shoes, with resultant traumatic inoculation of the feet by volcanic soil particles leading to lymphatic obstruction, to the development of endemic (African) KS, and even classic KS as well, but this remains speculative [9,10].
- **Iatrogenic/immunosuppression-related KS.** Transplant recipients placed on immunosuppressive medications, as well as others placed on similar medical regimens, are at increased risk for iatrogenic KS. The incidence of KS may be approximately 84-fold higher among organ transplant patients in comparison with the general population [11]. Most iatrogenic KS occurs at least 1–2 years after immunosuppressive medications are initiated [12]. While an aggressive course, with visceral involvement, can occur with iatrogenic KS, withdrawal of the immunosuppressive agent(s) may often yield disease regression and remission. Furthermore, the specific immunosuppressive agent(s) employed impacts risk. Sirolimus, in addition to immunosuppressive effects, possesses antineoplastic properties as well, and the agent has not been associated with the same elevated risk of KS seen in other immunosuppressive medications; in fact, it may even be employed in the management of iatrogenic KS [13]. Iatrogenic KS occurs more often among the same populations that are at risk for classic KS, suggesting the etiology may be multifactorial.

## Incidence/prevalence

The incidence of KS varies with the clinical subtype.

- Classic KS is rare, but is most common in older men, with an M:F ratio of up to 15:1. Peak onset occurs at 50–70 years of age.



Figure 36.1 Classic KS, with edema of the left leg.



Figure 36.3 Extensive AIDS-related KS.

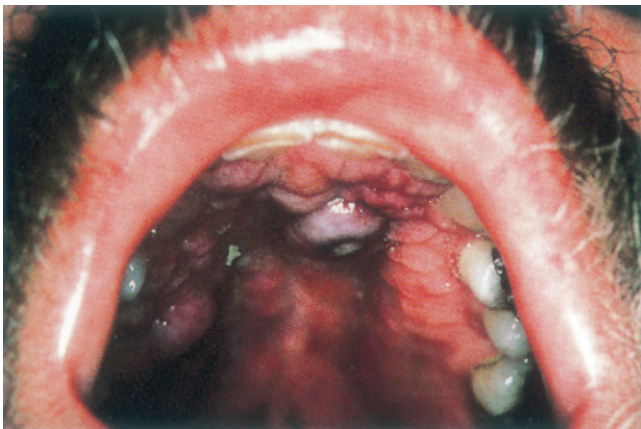


Figure 36.2 KS affecting the hard palate in a patient with AIDS.

The disease is particularly prevalent in Israel and the Mediterranean, including southern Europe. In fact, in southern Italy, the incidence rate of classic KS range may be as high as 24–30 cases per million in men, and five to eight cases per million in women [14].

- Epidemic AIDS-related KS is the most common form of KS, worldwide. In the USA, the incidence of AIDS-related KS reached its zenith in 1989, when it was the most common AIDS-related neoplasm, and its incidence has declined since then, particularly with widespread adoption of HAART [15]. The incidence among men outside of the San Francisco area manifested a profound decrease, dropping from 7.9 to 1.6 cases per 100 000 [16]. Similarly, a European multicenter cohort study of nearly 10 000 HIV-positive patients reported an estimated annual reduction of 39% between 1994 and 2003 for epidemic (AIDS-related) KS among patients receiving HAART [17]. Overall, the incidence of KS among patients with HIV is less than 10% of the incidence reported in 1994.



Figure 36.4 Endemic (African) KS.

- Endemic (African) KS is a relatively common tumor in sub-Saharan Africa, and there has been an increased incidence and a narrowing of the M:F ratio over time, moving from a historic ratio of 19:1 (1960–1971) to the more modern ratio of less than 2:1 (1991–1997) [18]. In fact, in many parts of Africa, KS is now the most common cancer in men and the second most common in women [19].



- Iatrogenic KS among transplant recipients has been estimated at 8.8 per 100 000 person-years in the USA, with most cases occurring in the first 2 years after transplantation, and the risk of KS increases steadily with recipient age ( $P = 0.001$ ) [20].

### Etiology

An infective etiology for KS was long suspected, but a milestone in understanding came in 1994, when Chang *et al.* identified sequences of HHV8 DNA, within tumor material [3]. Since that time, the virus has been detected in virtually all KS specimens, regardless of subtype, but has been absent from uninvolved skin. The viral genome encodes proteins that are homologous with human oncoproteins and have the potential to induce cellular proliferation and inhibit apoptosis. The presence of HHV8 appears requisite to development of KS, but the role of other permissive cofactors, such as immunosuppression, other cytokines, and HIV, is still being investigated and debated.

As a malignancy, it was long presumed that KS was caused by the clonal expansion of a single endothelial cell, but recent evidence may suggest otherwise. For example, the cell of origin is still unproven, and expression of multiple immunohistochemical markers among KS cells, including factor VIIIa, smooth muscle actin, CD68, and CD14, as well as lymphatic markers, such as D2-40, in addition to common vascular markers of CD31 and CD34, may also be interpreted to suggest the origin is a pluripotent mesenchymal progenitor cell [21,22].

Similarly, data from a series of patients with multiple lesions of KS showed that nearly 80% of the tumors were polyclonal in nature, engendering speculation that “metastatic” KS may not be truly metastatic (in the strict sense), but may be multifocal, arising independently at various sites [23].

### Diagnosis/histology

The diagnosis of KS is typically made based upon clinical suspicion, and then confirmed with a biopsy and histopathologic analysis. While the fundamental qualities of a malignant spindle cell neoplasm are common to all forms KS, clinical circumstances, as well as the temporal course of the lesion, will clearly impact the histologic findings in cutaneous disease [24].

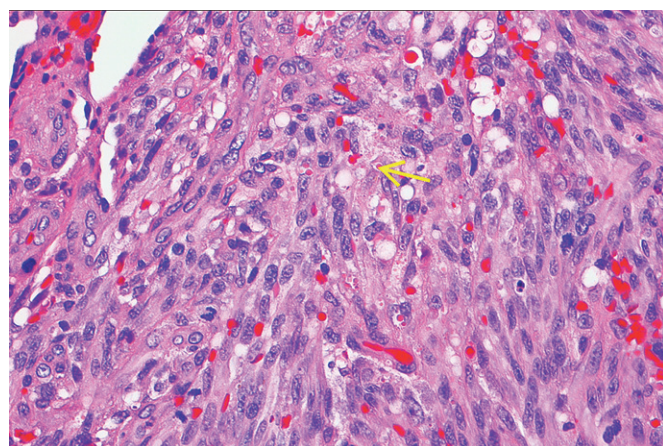
- **Patch stage.** The earliest phase in the evolution of typical cutaneous KS, patch stage disease, also presents the greatest degree of diagnostic difficulty owing to the subtle nature of the findings. Often, the dermis only appears only slightly hypercellular, with subtle and slit-like or jagged vascular spaces present upon close inspection. The protrusion of newly formed rudimentary vascular structures into the lumen of larger vascular channels results in a “promontory sign.” Proliferating vessels may dissect the collagen, and often there are a varied number of extravasated erythrocytes and hemosiderin-laden macrophages. Background inflammatory cells, mostly lymphocytes and plasma cells, may be present.

- **Plaque stage.** This is accompanied by greater cellularity and perhaps even extension of neoplastic process into the subcutis. Atypical spindled cells are arranged in haphazard fascicles. Mitotic figures may be present, and extracellular perioic acid Schiff-positive hyaline globules, thought to represent fragmented and decaying erythrocytes, may be noted [25]. Dissecting vascular channels with central erythrocytes exist in the dermis, and an inflammatory infiltrate rich in plasma cells is common.

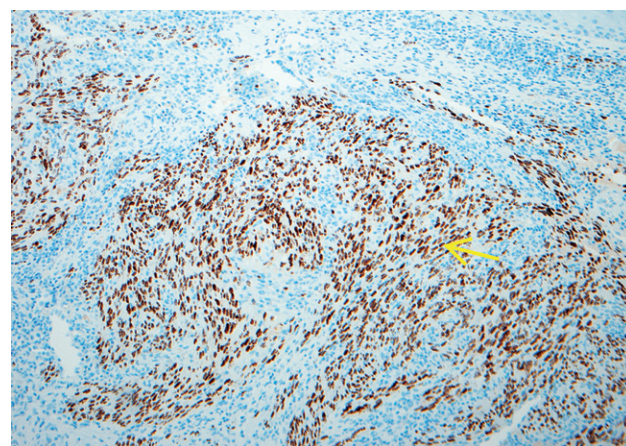
- **Nodular stage.** Nodular disease usually results in marked dermal expansion of atypical spindled cells arranged in fascicles (Figure 36.5). These spindled cells are monomorphic and atypical in appearance. Mitotic activity among the cells is not uncommon. Hyaline globules, also seen in plaque-stage disease, are typically rather numerous in nodular KS. At the periphery of nodular lesions there are often dilated and congested vascular spaces.

Other recognized and described variants of KS, beyond the scope of this discussion, but more germane to a text on dermatopathology, include hyperkeratotic, keloidal, micronodular, pyogenic granuloma-like, ecchymotic, and intravascular forms [24].

Immunohistochemical stains that may prove useful in confirming a histologic assessment of KS include use of antibodies directed at the alleged endothelial/lymphatic origin of the spindled cells, such as CD31 (platelet/endothelial cell adhesion molecule, PECAM1), CD34 (a hematopoietic progenitor cell surface protein), D2-40 (podoplanin, a cell surface marker of lymphatic endothelium), and FLI1 (Friend leukemia virus integration 1, a member of the ETS family of DNA-binding transcription factors). A recent



(a)



(b)

**Figure 36.5** Histologic and immunohistochemical analysis of nodular KS: (a) stained with H&E, shows atypical spindled cells and extravasated erythrocytes and pink hyaline globules (arrow). (b) stained with an immunohistochemical marker for HHV8, shows strong and aberrant positivity among the atypical spindled cells (arrow).

investigation of these four antibodies (CD31, CD34, D2-40, and FLI1) strongly and diffusely stained tumor cells in 75%, 92%, 67%, and 92% of AIDS-related cases, and 58%, 92%, 67%, and 75% of non-AIDS-related cases, respectively [26]. Additionally, a commercially available monoclonal antibody directed against HHV8, for use on formalin-fixed, paraffin-embedded tissue, has been available since 2004. One such clone, directed against the virus latency-associated nuclear antigen of HHV8, has demonstrated high sensitivity and specificity for all clinical subtypes and tumor stages of KS, and is of great utility, especially in subtle patch-stage disease [27].

Prognosis

The prognosis for KS varies depending upon the clinical subtype, the extent of tumor and/or organ involvement, and the overall general medical condition of the patient.

- Classic KS usually follows a rather indolent course that spans years or decades. Complications include venous stasis, lymphedema, and verrucous and/or hyperkeratotic qualities to the epidermis overlying KS lesions. Admittedly, many of these conditions, to one degree or another, are not unexpected upon the lower legs of elderly persons with circulatory issues (even absent KS). It is widely held that persons with classic KS often die “with the disease,” rather than “of the disease.”
- Epidemic (AIDS-related) KS may be a disseminated and fulminant disease. The tumor extent (T), immune status (I), and severity of systemic illness (S) are all expected prognostic determinants. To this end, in the pre-HAART era, a TIS staging classification was proposed and prospectively validated (Table 36.1) [28]. Even in the HAART era, only minor alterations of these prognostic factors are proposed. For example, CD4 count of <200 cells/ $\mu$ L and tumor extension are no longer negative prognostic factors, but a CD4 count of <100–150 cells/ $\mu$ L and associated systemic

diseases are important considerations in patients taking HAART [29,30].

- Endemic (African) KS may run an indolent course similar to that of classical KS, with nodules and plaques occurring in association with limb edema. In particular, some cases of lymphadenopathic endemic (African) KS occurring in children in Africa may follow an aggressive clinical course, with an adverse prognosis [31].
- Iatrogenic KS may often substantially improve or even regress following reduction or removal of immunosuppressive medications [32,33].

Therapeutic goals

Similar to prognosis, the goals of therapy vary with the clinical form of disease, the extent of disease, and the general medical health of the patient with KS.

- Classic KS often responds quite well to local interventions, although the recurrence rate is high.
- Epidemic (AIDS-related) KS is improved significantly by the addition of HAART, which prolongs overall survival and is associated with an 80% reduction in the risk of death [34], prolongs the time to treatment failure [35], and prolongs the survival of patients with pulmonary KS who receive also chemotherapy [36]. It is unclear exactly how HAART induces regression of KS, but potential mechanisms are thought to include immune reconstitution [37], general improvement in the immune status, and perhaps even direct anti-angiogenic and antineoplastic effects [38].
- Endemic (African) KS usually responds well to systemic interventions, except for aggressive lymphadenopathic forms.
- Transplantation-related or immunosuppression-related KS often regresses after the reduction or cessation of immunosuppressive medications.

Relevant outcomes

Complete disappearance of the disease is the most obvious relevant outcome, but it is not always achieved or reported in trials regarding the treatment of KS. A reduction in the number and/or size of lesions, lesion flattening, and reduction in pigmentation may represent other measured endpoints. The subjective nature of many assessments is a shortcoming in the comparison of treatments. To this end, AIDS Clinical Trials Group (ACTG) criteria were developed for use in clinical trials (Table 36.2) [39]. In fact, modified variants of the original ACTG criteria are still currently employed in the most recent clinical trials [40]. Furthermore, improved cosmesis, while markedly subjective, is also an important endpoint for affected patients, particularly with regard to localized interventions. Lastly, palliation of tumor-related symptoms, such as edema or pain, is another endpoint that, while highly subjective, is valued by patients.

Methods of search

We searched Medline from 1966 to December 2012. We first performed a highly sensitive search using the truncated term “Kaposi\*,” which generated over 10 000 abstracts. We then performed a more specific Medline search using “sarcoma, Kaposi” (MeSH terms) or “Kaposi’s sarcoma” (text word), combined with the following interventions: alitretin, antiretroviral therapy, anthracycline, antiangiogenic agent, bleomycin, chemotherapy, cidofovir, gemcitabine, highly active antiretroviral therapy, interferon (IFN), intralesional therapy, intralesional vinblastine, intralesional vincristine, paclitaxel, radiotherapy, retinoids, vinca-alkaloid, vincristine,

Table 36.1 ACTG staging classification.

Good risk (0): all of the following		Poor risk (1): any of the following
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease <sup>a</sup>	Tumor-associated edema or ulceration
		Extensive oral KS
		Gastrointestinal KS
		KS in other nonnodal viscera
Immune system (I)	CD4 count $\geq 200 \times 10^6/L^b$	CD4 count $< 200 \times 10^6/L^\ddagger$
Systemic illness (S)	No history of opportunistic infections or thrush	History of opportunistic infections and/or thrush
	No “B” symptoms <sup>c</sup>	“B” symptoms present
	Performance status $\geq 70\%$ (Karnofsky)	Performance status $< 70\%$
		Other HIV-related illness (e.g., neurological disease, lymphoma)

<sup>a</sup>Minimal oral disease is KS, without a nodular appearance, confined to the palate.  
<sup>b</sup>Subsequent evidence suggests CD4 count of  $150 \times 10^6/L$  may be a superior discriminator.  
<sup>c</sup>“B” symptoms are unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting for more than 2 weeks.



**Table 36.2** ACTG response criteria.**Complete response (CR)**

The absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks

**Clinical complete response (CCR)**

In patients in whom pigmented (brown or tan) macular skin lesions persist after apparent CR, biopsy of at least one representative lesion is required to document the absence of malignant cells. In patients known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made. If such procedures are medically contraindicated, the patient may be classified as having CCR

**Partial response (PR)**

The absence of new cutaneous or oral lesions, new visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions, in addition to at least one of the following:

- A 50% or greater decrease in the number of all previously existing skin lesions (skin, oral, measurable or evaluable visceral disease)
- A 50% decrease in the size of lesions (includes a 50% decrease in the sum of the products of the largest perpendicular diameters of bidimensionally measurable marker lesions and/or complete flattening of at least 50% of the lesions; that is, 50% of previously nodular or plaque-like lesions become macules)
- In those patients with predominantly nodular lesions, flattening to an indurated plaque of 75% or more of the nodules
- Patients with residual tumor-associated edema or effusion who otherwise meet the criteria for CR

**Stable disease (SD)**

Any response not meeting the criteria for progression or PR

**Progressive disease (PD)**

An increase of 25% or more in the size of previously existing lesions, and/or the appearance of new lesions or new sites of disease, and/or a change in the character of 25% or more of the skin or oral lesions from macular to plaque-like or nodular. The development of new or increasing tumor-associated edema or effusion is also considered to represent disease progression

vinblastine, taxane, paclitaxel, retinoids, retinoic acid, zidovudine. We also searched the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews using the search terms “Kaposi\*” and “Kaposi’s sarcoma.”

## Questions

### What are the effects of local treatments commonly employed in management of Kaposi sarcoma (radiotherapy, topical alitretinoin, topical imiquimod, intralesional interferon and intralesional chemotherapy)?

#### Radiotherapy

There are numerous case reports and case series employing radiotherapy as local intervention for classic KS, and it is a radiosensitive condition. In most of these publications the patients were treated with either local or extended-field radiotherapy, or local electron beam. High response rates (80–90%) were reported; however, response criteria were not always well stated, and/or varied among reports.

In epidemic (AIDS-related) KS there are a few published trials comparing different radiotherapy regimens.

- One trial compared 71 lesions of biopsy-proven KS, occurring in 14 AIDS patients (seven taking zidovudine, but none taking HAART) [41]. KS lesions were randomized to receive either 8 Gy in one fraction, 20 Gy in 10 fractions, or 40 Gy in 20 fractions. The trial was not blinded and randomization criteria were not stated. Results were assessed on an intention-to-treat (ITT) basis. A complete response was the principle endpoint, defined as resolution of all palpable tumor in the radiation field. Improved results were observed in lesions dosed with either 40 Gy given in 20 fractions, or 20 Gy given in 10 fractions, when compared with those dosed with 8 Gy in a single fraction (83% and 79% vs 50%). Median recurrence times were improved as well (43 and 26 weeks vs 13 weeks). Adverse events were more common in lesions treated with 20 or 40 Gy than in those treated with a single dose of 8 Gy.
- A second trial involved the comparison of conventional fractionated radiotherapy with a hypofractionated regimen [42]. Sixty-five evaluable lesions in 47 patients with AIDS-related cutaneous KS were randomized to receive either a standard regimen of 24 Gy in 12 fractions (35 sites), or 20 Gy in five fractions (30 lesions). Some patients expired prior to irradiation, but the treatment arms were similar with regard to gender, Eastern Cooperative Oncology Group performance score, anatomic site, and use of concurrent antiretroviral therapy. With regard to the response observed (complete or partial) or the mean time to a maximum objective response, there were no significant differences among the two treatment arms, and skin toxicity (acute or chronic) was also equivalent.

#### Drawbacks

In the earlier trial, toxicity was graded using the Radiation Therapy Oncology Group scoring system. Grade 1 acute toxicity (skin erythema, dry desquamation, or alopecia) was seen in 3 of 24 (12%) patients who received 8 Gy, 11 of 24 (46%) patients who received 20 Gy, and 22 of 23 (96%) patients who received 40 Gy. Late skin toxicity, again not to exceed grade 1 (slight hyperpigmentation or alopecia), occurred only in patients receiving 40 Gy (six of 23).

In the later trial, where a hypofractionated dose of 20 Gy was compared with a conventional fractionated dose of 24 Gy, skin toxicity was statistically equivalent among the groups, the investigators advised caution when employing the hypofractionated regimen in patients with severe lymphedema, as four patients receiving this latter regimen developed ulceration or necrosis.

#### Comments and implications for practice

Radiotherapy, either in a local or extended field, and either highly fractionated or hypofractionated, yields a high response rate in the treatment of KS. In AIDS patients this intervention is still widely employed, especially to control oral disease. The rate of complete response and the duration of control may be improved with higher dose and highly fractionated radiotherapy; however, shorter treatment regimens are resource sparing, and benefit patients in health systems that are unable to bear the costs of prolonged treatment. Also, larger doses per fraction in radiotherapy may result in increased toxicity. Additionally, in the era of HAART, a decision to treat may also be influenced by use of concurrent antiretroviral therapy.

#### Topical alitretinoin

Alitretinoin (9-*cis*-retinoic acid) gel is a retinoid receptor pan-agonist that was pursued about a decade ago as treatment of

cutaneous KS. A Cochrane review examined two trials of topical alitretinoin used as treatment in patients with epidemic (AIDS-related) KS [43], but the results could not be combined owing to heterogeneity. Without belaboring details, both trials indicated safe and effective use, and irritation was the major drawback, but the overall response rates were modest [44,45]. While approved for this indication, the drug is not in widespread clinical use for treatment of KS. While occasional case reports of success and failure continue to be published, no organized clinical investigation of this agent for treatment of KS has transpired since 2003 [46].

### Intralesional interferon

Because of its antiviral effect, intralesional IFN- $\alpha$  has been investigated for use in the treatment of KS.

- A small clinical investigation examined use of intralesional and perilesional IFN- $\alpha$  (50 000 international units twice weekly for 4–6 weeks) to treat non-AIDS-related KS in 12 patients, and compared this regimen with an untreated lesion in the same patient. An additional treatment arm investigated use of IFN- $\alpha$  in combination with interleukin-2 in eight additional patients, again comparing the combined intervention with an untreated lesion in the same patient [47]. All the treated lesions yielded complete resolution, while all the untreated lesions remained unchanged, and the observed clinical cure was then verified histologically. Investigators concluded that intralesional IFN- $\alpha$  is an effective treatment for non-AIDS-related KS.
- In a small study of 17 patients with epidemic (AIDS-related) KS who were receiving zidovudine (500 mg/day), up to five KS lesions per patient were injected with IFN- $\alpha$  (1 million units three times weekly for 6 weeks) and compared this therapy with another lesion in the same patient that was injected with sterile water [48]. Three patients were lost to follow-up and three patients were injected only with IFN- $\alpha$  because just one lesion was present. In brief, a complete response was seen in 41 of 54 (76%) treated lesions, in comparison with three of 11 (27%) lesions injected with sterile water. ITT results were neither provided nor calculable. On biopsy, two of 15 (13%) lesions injected with IFN- $\alpha$ , and one of two lesions injected with sterile water but for which a clinical response was observed, were found to have microscopic evidence of persistent KS.

### Drawbacks

Patients placed upon systemic IFN- $\alpha$  experienced flu-like symptoms. Local pain and inflammation at the injection site was common. Published regimens required two to three visits per week for up to 6 weeks.

### Comments

Intralesional IFN- $\alpha$  is not often used in clinical practice for epidemic (AIDS-related) KS, especially in the era of HAART (see below).

### Intralesional chemotherapy

In the literature of oral medicine, a small randomized trial compared intralesional vinblastine and 3% sodium tetradecyl sulfate (STS), a sclerosing agent, as a treatment for oral epidemic (AIDS-related) KS [49]. A similar reduction in tumor mass was observed for both agents, and it was concluded that both agents were effective in controlling the condition. STS was associated with a lower cost and greater ease of use.

### Comment

Intralesional vinblastine (0.1–0.2 mg/mL) has been used in several case series of patients with cutaneous epidemic (AIDS-related) KS, with reported response rates ranging from 60 to 92%. In particular, intraoral lesions of epidemic (AIDS-related) KS has been treated with particular efficacy using this agent.

### Topical imiquimod

#### *Classic and endemic (African) Kaposi sarcoma*

Because KS can be treated with intralesional IFN- $\alpha$ , it was hypothesized that imiquimod, a topical immune response modifier that induces endogenous production of IFN and related substances, would be efficacious in treating the disorder. In one prospective, open-label, single-center, phase I to phase II trial, topical imiquimod 5% cream was utilized in the management of classic or endemic (African) KS skin lesions in HIV-negative patients [50]. Topical imiquimod 5% cream was applied under occlusion three times a week for 24 weeks in 17 enrolled patients. Results were analyzed in ITT format, and there were eight (47%) with an overall clinical response (two complete, six partial), while progression was noted in six patients.

**Drawbacks** Side effects included local itching and erythema, reported in nine patients (53%).

**Comments** This trial was not randomized, it was not blinded, and it was not placebo controlled. It was restricted to a small number of patients. While topical imiquimod 5% cream was efficacious in only about one-half of patients with classic and endemic (African) KS, it was generally well tolerated and it is widely available to the practicing dermatologist.

### Is interferon- $\alpha$ an effective systemic treatment for Kaposi sarcoma?

#### *Classic and endemic (African) Kaposi sarcoma*

No randomized clinical trials were found. Only case reports and small case series were found in the literature.

### Comment

Data are insufficient to draw firm conclusions regarding the effectiveness of systemic IFN- $\alpha$  in the treatment of classic or endemic KS.

### Epidemic (AIDS-related) Kaposi sarcoma

Phase II trials demonstrated the efficacy of high-dose IFN as a monotherapy for epidemic (AIDS-related) KS. Side-effects of such treatment included dose-related phenomena, such as flu-like symptoms, but gradual dose escalation ameliorated this toxicity [51,52].

Multiple phase II trials performed subsequently examined the treatment of epidemic (AIDS-related) KS using a combination of IFN- $\alpha$ , at low or intermediate doses, with zidovudine. Relatively low doses of IFN- $\alpha$  (in comparison with those used as monotherapy) proved efficacious if combined with zidovudine, and suggested relative efficacy, even in patients with CD4 counts <200/ $\mu$ L, a population that had responded poorly to high IFN alone [53,54]. A similar phase II trial of 68 patients examined the efficacy of low and intermediate doses of IFN- $\alpha$ -2b in combination with didanosine (ddI), and a 40% response was observed in the low-dose group (95% confidence interval [CI], 24–58), with a 55% response rate in

the intermediate-dose group (95% CI, 36–72) [55]. Median duration of remission was 110 weeks in both groups.

### Comments

The advent of HAART has altered substantially the clinical course of epidemic (AIDS-related) KS. The effectiveness of IFN combined with HAART is unknown. Use of zidovudine or ddI alone is no longer standard therapy for HIV infection.

## What are the effects of systemic chemotherapy employed in Kaposi sarcoma?

### Classic Kaposi sarcoma

We found one randomized but unblinded study comparing oral etoposide with intravenous vinblastine in the treatment of classical KS in elderly Mediterranean patients [56]. Sixty-five patients were assigned randomly to receive either oral etoposide (60 mg/m<sup>2</sup> on days 1–3 during the first course; 60 mg/m<sup>2</sup> on days 1–4 during the second course; and 60 mg/m<sup>2</sup> on days 1–5 during the third course; courses were recycled every 3 weeks) or intravenous vinblastine (3 mg/m<sup>2</sup> weekly for 3 weeks, and then 6 mg/m<sup>2</sup> every 3 weeks). With a median follow up of 38 months, there were no statistically significant differences in number of complete or partial responses, in the duration of response, or in survival. Side effects of both agents were limited, although myelotoxicity was more evident in those patients receiving vinblastine.

### Comment

Neither agent is used often to treat classic KS.

### Epidemic (AIDS-related) Kaposi sarcoma

A Cochrane systematic review of treatments for AIDS-KS [43] included two randomized and unblinded studies comparing pegylated liposomal doxorubicin (PLDox) with standard treatment regimens in patients with advanced KS [57,58]. Randomization methods were not detailed for either study, and analysis occurred on an ITT basis. Meta-analysis of these two studies yielded a total of 499 patients treated with PLDox, versus a standard KS regimen using either doxorubicin, bleomycin, and vincristine (ABV, first trial), or bleomycin and vincristine (BV, second trial). No participant, in either study, was receiving HAART. The relative risk (RR) of death was not significantly different for either of the two treatments (RR, 1.26; 95% CI, 0.83–1.91), and the response to PLDox was superior to that of the ABV/VB in each trial (RR, 2.16; 95% CI, 1.68–2.78). Adverse events were reported in different ways and could not be analyzed together, but serious adverse events did not differ significantly between the PLDox (RR, 0.97; 95% CI, 0.91–1.04) or the standard regimens (RR, 1.01; 95% CI, 0.96–1.06). Fewer withdrawals occurred in the PLDox-treated group (RR, 0.57; 95% CI, 0.48–0.68), but more opportunistic infections were observed (RR, 1.42; 95% CI, 1.12–1.80).

Another phase III trial of pegylated liposomal daunorubicin (PLDaun) versus a reference regimen of ABV in advanced epidemic (AIDS-related) KS was not included in the meta-analysis because it did not report results on an ITT basis [59]. In brief, this trial that could not be integrated to the meta-analysis was a prospective, randomized, phase III trial, including 232 patients who were randomly assigned to receive PLDaun 40 mg/m<sup>2</sup> or a combination ABV regimen administered intravenously every 2 weeks. Treatment was continued until a complete response (CR) or unacceptable toxicity was achieved, or tumor progression was observed. Of 232 patients randomized, 227 were treated. PLDaun was dosed to 116

patients, while 111 patients received ABV. A statistically significant difference in the response rate or median survival time was not observed among the treatment arms.

### Comments

Most low-risk patients, as defined by the ACTG, showed regression of epidemic (AIDS-related) KS lesions with HAART alone. High-risk patients often required a combination of HAART and chemotherapy, with discontinuation of chemotherapy upon disappearance of clinically relevant disease.

### Drawbacks

**Neutropenia** The most common adverse event in both arms of an RCT comparing PLDox with ABV chemotherapy was leukopenia, affecting 36% of 133 patients who received PLDox and 42% of 125 patients in the ABV group [58]. Grade 3 neutropenia, with an absolute neutrophil count (ANC) between 500 and 1000 cells/mm<sup>3</sup>, was similar in PLDaun- and ABV-treated groups (36% vs 35%, respectively), but grade 4 neutropenia (ANC < 500) was more common in the PLDaun-treated group within the same randomized trial (15% vs 5%;  $P = 0.021$ ) [59].

**Cardiotoxicity** Of 24 patients who received a cumulative dose of >500 mg/m<sup>2</sup> of PLDaun in one randomized study, none were found to have a 20% or greater decline in their left ventricular ejection fraction (LVEF) [59]. In another randomized clinical trial of PLDox versus ABV, pre- and posttreatment estimations of LVEF were available for 47 patients, and just two patients were found to have had a >20% decrease in LVEF [57]. In this same study, just one death was attributed to cardiomyopathy out of 133 patients treated with the PLDox. It would appear that, unlike traditional agents, the pegylated anthracyclines are not associated with marked cumulative cardiotoxicity.

**Nausea and vomiting** Of the patients receiving PLDaun, 51% experienced mild nausea [59]. Grade 3 nausea and vomiting were significantly more frequent with ABV than with PLDox (34% vs 15%;  $P < 0.001$ ) [57].

**Alopecia** In two different randomized trials for treatment of KS, alopecia occurred significantly more often among patients who received ABV chemotherapy than those who received pegylated anthracyclines [57,59].

**Peripheral neuropathy** In two different randomized trials for treatment of KS, peripheral neuropathy occurred significantly more often among patients who received ABV chemotherapy than those who received pegylated anthracyclines [57,59].

**Acute infusion reactions** In three studies of pegylated anthracyclines for KS, acute infusion reactions in just 2% (two of 116) and 5% (six of 133) and 4% (five of 121) patients [57–59]. These acute reactions included flushing, chest pain, hypotension, and back pain. In most cases, premedication to ameliorate these reactions allowed for continued use of pegylated anthracyclines [57], but in one case a severe anaphylactic reaction occurred with PLDox [58].

### Comments and implications for practice

Three large trials suggest that pegylated anthracyclines are at least as effective, if not more effective, in AIDS-related cutaneous KS as standard ABV or BV combination chemotherapy [57–59].

Furthermore, a superior toxicity profile exists for the pegylated anthracyclines. Although there are no randomized, controlled trials directly comparing the two liposomal agents (PLDox and PLDaun), there is reason to believe the response rate for patients with advanced epidemic (AIDS-related) KS may be higher with PLDox.

#### **Implications for practice**

Evidence suggests that PLDox is beneficial for the palliative treatment of advanced epidemic (AIDS-related) KS. Because of a superior toxicity profile, PLDox should be used as first-line systemic therapy for patients with advanced epidemic (AIDS-related) KS. However, the liposomal anthracyclines are quite expensive and are not readily available in developing countries. No recent trials of chemotherapy exist in the other types of KS, but case reports and case series suggest that classic KS or endemic (African) KS is as chemosensitive as AIDS-related disease.

#### **What are the effects of antiretrovirals in the treatment of epidermic (AIDS-related) Kaposi sarcoma?**

Three cohort studies (one small prospective cohort, one larger retrospective cohort, and one large prospective cohort) examined the effect of HAART on epidemic (AIDS-related) KS [60–62]. A small clinical trial compared HAART plus PLDox with the HAART alone [63].

#### **Efficacy**

HAART, which includes two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or one or two protease inhibitors, has altered substantially the natural history of epidemic (AIDS-related) KS. In fact, widespread adoption of HAART has greatly decreased the observed incidence of KS [34–36], and population-based studies throughout the world have demonstrated that HAART has decreased the incidence of KS as an AIDS-defining illness [64–66].

A small, randomized, open-label study compared HAART plus PLDox with HAART as treatment for moderate to advanced epidemic (AIDS-related) KS [63]. PLDox–HAART patients received a median of 11 cycles of intravenous PLDox treatment. After 48 weeks of follow-up, ITT analysis indicated that nonresponses, partial responses, and complete responses occurred in 4, 6, and 3 patients respectively in the HAART–PLDox group and in 2, 1, and 12 patients in the HAART-alone group, respectively ( $\chi^2$  test 9.5;  $P = 0.008$ ), with a significant difference in the number of partial responders with PLDox–HAART. The investigators concluded that HAART therapy alone does not provide adequate treatment for some patients with moderate to advanced KS.

In a more recent and larger prospective cohort, the effect of HAART was examined in 254 consecutive patients (96% men) diagnosed with epidemic (AIDS-related) KS between 1996 and 2008 (with a median follow-up of over 4 years) [62]. At the time of diagnosis of KS, only 19% patients were on HAART, and only 7% patients had an undetectable plasma viral load for HIV. HAART alone was utilized for management in 163 patients with KS (stage T0), and only one died of KS. Only 37 patients (22%) required adjunctive chemotherapy, yielding a systemic treatment-free survival at 5 years of 74% (95% CI, 67–82), and an overall survival at 5 years of 91% (95% CI, 87–95). The investigators concluded that there was a high success rate of HAART alone in a large cohort of AIDS patients with KS, followed over a prolonged period time, and

that this approach is both well tolerated and effective, particularly for KS (stage T0).

This more recent work augmented an earlier, smaller, prospective cohort study, involving 39 patients with epidemic (AIDS-related) KS treated with HAART, that reported complete and partial response rates of 46% and 28% at 24 months utilizing this treatment modality alone [60]. Additionally, retrospective analysis had already documented a reduced time to relapse of epidemic (AIDS-related) KS when HAART was initiated (0.5 years vs 1.7 years) [61].

#### **Drawbacks**

The side effects profile of HAART depends chiefly upon the individual drugs used and any potential interactions with other drugs the patient is taking. More common side effects include nausea, vomiting, lethargy, diarrhea, peripheral neuropathy, headache, aberrant liver function and elevation of transaminases, hypersensitivity reactions, myelosuppression, lactic acidosis, and pancreatitis.

#### **Implications for practice**

HAART prevents development of KS in patients with HIV, and it has also dramatically decreased the incidence of KS as an AIDS-defining illness. There is evidence that HAART alone may induce regression of individual KS lesions through different postulated mechanisms (immune reconstitution, inhibition of HIV replication, anti-angiogenic and anticytokine effects). Patients with high viral loads, low CD4 counts, or with other HIV-related symptoms require antiretroviral therapy for control of HIV infection. HAART alone in these patients is a reasonable initial therapy for KS, which may be combined later with other local or systemic treatments, particularly in those with more extensive and/or aggressive disease.

#### **Key points**

- HAART therapy has had a significant impact in decreasing the prevalence and severity of epidemic (AIDS-related) KS.
- For many cases of epidemic (AIDS-related) KS, initiation of HAART therapy alone may be adequate therapy, although occasionally moderate to severe disease will require an adjunctive intervention.

#### **Local therapy**

- In classic KS and epidemic (AIDS-related) KS, radiotherapy is likely to improve cosmetic outcome of individual cutaneous lesions, with minimal harm. The optimum dose fractionation schedule in these conditions is yet to be determined, and is beyond the domain of dermatology, but with hypofractionated regimens the potential cutaneous side effects and/or complications may be more substantial.
- Topical imiquimod may have some modest efficacy in treating KS, and it is a drug widely available and familiar to the practicing dermatologist.

#### **Systemic therapy**

- Systemic IFN- $\alpha$  is likely to be beneficial for some cases of epidemic (AIDS-related) KS and this agent can be safely combined with antiretroviral therapy.
- This regimen would seem best suited as first-line therapy for patients with CD4 counts  $>200 \times 10^6$  cells/L, no “B-type” symptoms, and no history of prior opportunistic infections.
- Evidence exists that PLDox is more effective in epidemic (AIDS-related) KS than standard combination chemotherapy.
- Unlike conventional anthracyclines, liposomal anthracyclines do not appear to be associated with cumulative cardiotoxicity.



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# Melanocytic nevi

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## Background

### Definition

Melanocytic nevi are benign proliferations of melanocytes located at different skin levels. Acquired nevi are generally smaller than 1 cm, whereas congenital ones are usually larger [1]. Pigmentation in different shades of brown can range from a brown–yellowish to brown–blackish color; sometimes – as in mature cellular nevi – they can be skin-colored.

### Classification

Melanocytic nevi, either congenital or acquired, can be classified relative to the histological location of melanocytes into a:

- *junctional nevus*, if the melanocytes are located at the dermoepidermal junction;
- *dermal nevus*, if the melanocytes are in the dermis;
- *compound nevus*, if the melanocytes are at both of the above locations.

A new clinical classification for acquired nevi has recently been proposed, based on dividing them into common and atypical nevi; this approach is particularly useful for stratifying the risk of melanoma. *Common nevi* are neoformations with a maximum diameter of 6 mm, with symmetrical shape and with a homogeneous pigmentation. *Atypical nevi* instead have a larger diameter and at least two of the following parameters: irregular borders (edges) and/or not well defined, asymmetric shape, irregular pigmentation, erythema, and accentuation of the cutaneous design (Figure 37.1) [2]. It is also possible to diagnose an atypical nevus when some or all of the “ABCD” criteria for melanoma diagnosis are present: asymmetry, irregular borders, heterogeneous color, diameter larger than 6 mm [3]. Using this definition, it can sometimes be very difficult to distinguish between atypical nevi and early melanoma, even with the adoption of recent noninvasive techniques such as dermoscopy [4]. In doubtful cases of this type, the lesions should be removed for histological verification.

A congenital nevus is a “melanocytic nevus that has existed since one’s birth”; however, a lesion with the same clinical and pathological characteristics as a congenital nevus can also appear within the first 2 years of life. In this case it is called “nevus tardive” [5].

Congenital nevi are normally classified in accordance with diameter into small (<1.5 cm), medium (1.5–19.9 cm), and large

(>20 cm); the so-called giant nevi are congenital nevi that involve entire anatomic areas (Figure 37.2) [6].

In congenital nevi, melanocytes are typically located on the lowest two-thirds of the dermis. Occasionally, they extend into the subcutaneous tissue, with isolated cells or groups of cells within the reticular dermis collagen fibers, with a tendency to be located around cutaneous appendages. However, many congenital nevi do not show these histopathological characteristics, resulting in a picture not dissimilar to that of acquired nevi; this happens most frequently with small congenital nevi [7].

### Incidence, prevalence, and etiological factors

In people with the same complexion (i.e., similar skin and eye color and ability to tan), the average nevus density varies in accordance with sun exposure. A study on English twins reported that those who spent at least 410 days by the sea in sunny places had 41 nevi/m<sup>2</sup> on average, whereas those who did not expose themselves at all only had 24 nevi/m<sup>2</sup>. Larger acquired nevi (≥5 mm) were more common in boys than in girls [8].

A multicenter Italian study on 3127 13–14-year-olds found a higher nevus density in body areas usually exposed to the sun (i.e., face or neck), becoming lower in density in areas of intermittent exposure, and with the lowest density in areas never exposed. A positive correlation was also reported between the number of sunburns and nevus density [9].

Genetic factors are also an important predictor of nevus development. A recent study based on 221 pairs of teenage twins suggested that genetic factors accounted for about 65% of nevus development, involving factors associated with eye color (7%), hair color (6%), and skin color (1%); the remaining 51% appears to be due to other as yet unidentified genetic factors [10].

A multivariate analysis reported that the use of sunscreens does not prevent the development of melanocytic nevi; however, a negative correlation between the amount of clothing used and nevus counts has been found [11]. Sunscreens are discussed in more detail in Chapter 30.

It has been estimated that 1% of newborns have a congenital nevus of any size, whereas giant congenital nevi are very rare. One study including over 500 000 newborns has shown that only one baby in 20 000 has a nevus with a diameter larger than 10 cm [12].



**Figure 37.1** The leg of a child with numerous common and atypical nevi.

Recent longitudinal studies looking at young children further indicate a linear increase, with respect to age, in the density and number of nevi between the ages of 6 and 12, with the rate of increase being higher in boys than in girls [13].

### Disease associations

Various disease associations have been reported with congenital nevi, particularly the larger ones. Leptomenigeal melanocytosis (associated with congenital nevi on the head and neck), meningo-myelocoele, and spina bifida (associated with nevi in the lumbosacral area) are just some of these associations.

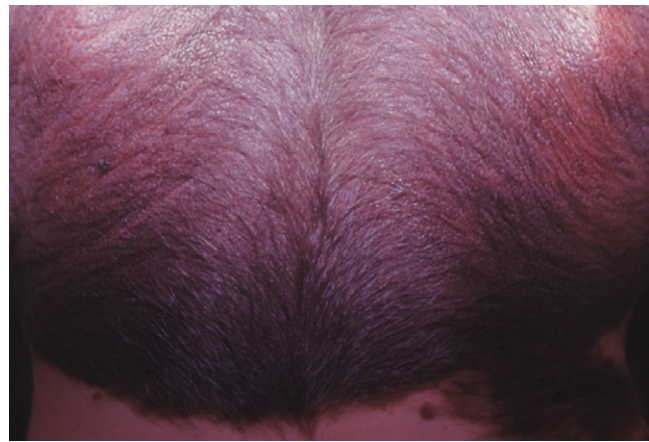
There are also reports in the literature of an association between nevi and ocular malformations and glaucoma, auricular malformation, angiomatous lesions, bone atrophy, and neurofibromatosis [7].

### Prognosis

The natural history of melanocytic nevi is still not fully understood. For acquired nevi, an initial development stage is observed within the first two to three decades of life, with an increase in nevus density afterwards, followed by a plateau. Then, in older age, there appears to be a density reduction, probably due to spontaneous regression of some nevi.

Melanocytic nevi can sometimes regress spontaneously during childhood or adolescence. This premature regression is commonly due to immunological mechanisms, as observed when a ring of depigmentation occurs around the nevus (halo or Sutton's nevus).

It is worth mentioning that some varieties of nevi arise at specific ages. For example, the Spitz nevus typically develops in childhood, while Reed's spindle-cell nevus typically occurs in women in their thirties.



**Figure 37.2** Large congenital nevus of the trunk in a girl (13 years old). The lesion is checked every 6 months.

## Diagnosis

### Clinical examination

Most nevi are easy for expert dermatologists to diagnose by clinical examination alone [14]; whenever there are doubtful cases (differential diagnosis with melanoma), dermoscopy (also known as dermoscopy or epiluminescence microscopy) can be performed in order to increase the diagnostic accuracy. However, dermoscopy is not 100% accurate, and if there is any remaining diagnostic doubt, an excisional biopsy followed by histological examination is recommended. An incisional biopsy is sometimes carried out if the lesions are very large.

### Dermoscopic examination

Dermoscopy is a noninvasive technique that enables the observer to examine some morphological characteristics of the lesion that are not visible with the naked eye. In expert hands, dermoscopy improves the diagnostic accuracy for nearly all pigmented skin lesions in comparison with naked-eye examination [15,16].

Digital dermoscopy also makes it possible to record digital images of specific lesions. This may help in investigating the natural history of a lesion for research purposes, or to follow up a doubtful lesion in order to identify any early malignant behavior. However, the extent to which digital follow-up of a doubtful lesion should be considered an advisable procedure is still a matter of debate [17]. The use of digital follow-up instead of immediate excisional biopsy is associated with a small risk of leaving a melanoma unexcised, with serious consequences. The risk can increase if patients do not comply with regular follow-up surveillance [18,19].

With regard to the impact of adding dermoscopy to melanoma screening, one controlled randomized trial showed that dermoscopy is associated with a significant reduction in the biopsy rate in comparison with a control group undergoing conventional naked-eye examination only (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.30–0.88) [17]. It is possible, therefore, that large-scale use of dermoscopy in melanoma screening may be associated with increased specificity in the diagnosis of melanoma, with fewer false-positive cases and consequently fewer surgical excisions for the purpose of diagnostic verification.



## Relevant outcomes

There are three main reasons for removing a melanocytic lesion. The first is to prevent a possible melanoma when there is a doubtful lesion, the second is to relieve discomfort (e.g., a mole rubbing a bra strap), and the third is for cosmetic purposes. Removing clinically banal nevi in order to reduce the incidence of melanoma is disputable practice; the risk of malignant degeneration of a nevus is in fact extremely low.

## Controversy

The term dysplastic nevus describes a histological finding referring to potential precursors of melanoma, first coined in 1980 by Greene *et al.* in support of the multistep tumorigenesis theory [20–22]. The basis of this theory is credited to Leslie Foulds and describes tumor development and progression from histologically normal melanocytes moving to hyperplasia to nevus to dysplastic nevus and ultimately progressing to melanoma [22]. Similarly, it has been proposed that dysplastic nevi “fit nicely into the schema of progression from hyperplasia to dysplasia to neoplasia that is accepted in many epithelial tumor systems, both experimental and human” [20]. The controversy lies in that some published data lack empirical data to support a multistep tumorigenesis theory – citing hypothetical instead of evidence-based data [23].

Many argue the use of the term “Clark nevus” instead of “dysplastic nevus” [24], in honor of Wallace H. Clark who initially described dysplastic nevus; however, this is still up for debate [25].

Despite this, there is a lack of consensus amongst dermatologists in the use of proper nomenclature, and the term dysplastic nevus continues to refer to precursors to malignancy, by many [21]. Furthermore, the progression of dysplastic nevi to melanoma is implicit in the common practice of classifying nevus as mild, moderate, or severe. To make matters worse, the terms “dysplastic nevus” and “atypical nevus” have been used synonymously in the literature. Studies indicate that these terms are, in fact, not synonymous, making it essential to clarify the distinction between “dysplastic nevus” (which refers to histological findings) and “atypical nevus” (which refers to a clinical description) [26,27].

Many studies suggest that patients with dysplastic nevi are at a much higher risk of developing melanoma compared with the general population [28–32]; however, most dysplastic nevi will never progress to melanoma [33,34]. Additionally, recent studies show that this risk is no higher in patients with dysplastic nevi than it is in patients with common nevi [35–38].

## Management of dysplastic nevi

Practices among physicians differ considerably when it comes to the management of dysplastic nevi [39]. The majority of dermatologists recommend yearly examinations in these patients. Studies indicate that therapeutic treatments such as 5-fluorouracil [40], isotretinoin [41], imiquimod [42,43], tretinoin [44], and laser ablation [45] are not effective in getting rid of or treating dysplastic nevi.

Since moderate to low-grade dysplastic nevi are not likely to reoccur [46,47], it is not advised to perform re-excision without compelling evidence for malignancy through histological or clinical features, especially if the intent of the original biopsy was to remove the nevus in its entirety [48]. Similarly, prophylactic removal of atypical nevi has not been shown to reduce the risk of developing melanoma [49]. Studies indicate, however, that 86% of dermatologists aim to completely remove the entire dysplastic nevi as part of the biopsy, yet dysplastic nevi are re-excised based on positive histological margins by 67% of dermatologists [39]. We advise institu-

tions and dermatopathologists using the graded system of mild, moderate, and severely atypical that severely atypical nevi require a standard re-excision with 5 mm margins even if no margins are involved, histologically, in the original biopsy specimen.

The authors’ institution has devised an atypical nevus specialty clinic and working group that has devised this proposed algorithm in dealing with the management of this controversial area in cutaneous medicine (see Figure 37.3).

## Methods of search

The databases of the Cochrane Library, Medline, and Embase between 1951 and April 2013 were searched for articles that (a) studied the relationship between nevi and (b) the risk of subsequent melanoma in congenital nevi of various sizes. The search was carried out by combining the following key words: melanocytic nevi, dermoscopy, epiluminescence microscopy, skin self-examination (SSE) and epidemiology, case-control, meta-analysis.

## Questions

### What is the risk of a melanocytic nevus developing into a melanoma?

It has been suggested that, because the high frequency of melanocytic nevi contrasts with the low incidence rate of nevus-associated melanoma (about 20–30% of all melanomas) [50], the transformation of an acquired nevus into a melanoma should be considered a very rare event, with an estimate of about one nevus out of 200 000 per year for people younger than 40 years of age and one nevus out of 33 000 per year for men over 60 years of age [9]. Little is known about the role of malignant transformation of a preexisting nevus in determining the increased risk of melanoma in people with many nevi. According to a case-control study that compared the risk factor profile of patients with nevus-associated melanoma (cases) with that of patients with melanoma de novo (controls), a large number of nevi were associated with a significantly higher risk for melanoma in the former than in the latter group of patients [51]. A history of many sunburns was more strongly associated with nevus-associated melanoma than with melanoma de novo. This finding lends support to the role of sunburn in increasing the risk of neoplastic progression of nevus cells. These results are based on a single study and need to be confirmed by further independent studies.

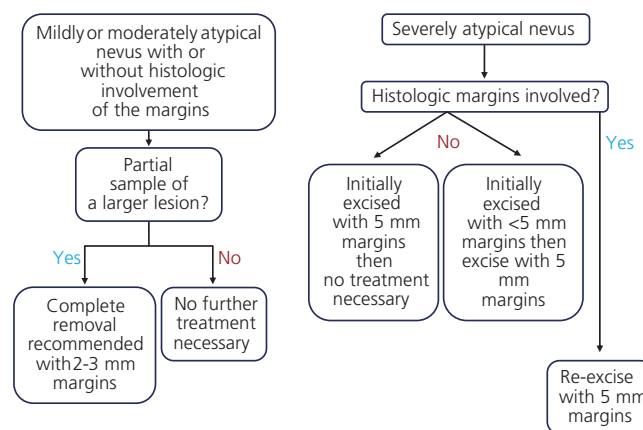


Figure 37.3 Algorithm for atypical nevus revision.

With regard to congenital nevi, their natural history appears to be strongly correlated with the lesion size. A prospective analysis of 80 children affected by large congenital nevi (diameter >20 cm) who were followed up for 5 years showed a malignant degeneration rate of 3.8% [52].

Subsequent research on 92 children (maximum age 3 years) with a large congenital nevus who were followed up for 5.4 years reported the occurrence of three melanomas, all of which were located in extracutaneous areas (the central nervous system and retroperitoneal region). This finding is explained by the possible existence of melanocytic hamartomas in noncutaneous areas such as the meninges and retina in some people with giant congenital nevi.

According to the data on giant melanocytic nevi, the risk of developing a melanoma within the first 5 years of life is 4.5% (95% CI, 0–9.3%), with a standardized incidence ratio over the expected number of the overall population equal to 239 [53].

More controversial than giant nevi is the behavior of congenital nevi with a diameter less than 20 cm. The transformation of intermediate (diameter between 1.5 and 19.9 cm) and small (diameter <1.5 cm) into melanoma is uncommon [54]. Though the specific risk is not currently known, recent prospective studies did not find any associations [55,56]. Still, some authors suggest that malignant transformation of such medium-sized lesions rarely if ever occurs before adulthood [52]. Further prospective cohort studies are needed to provide reliable data on the malignant transformation rate of small and intermediate-sized congenital nevi.

### **How should a patient with an isolated congenital nevus be managed?**

There are no widely accepted guidelines on how to deal with congenital nevi [57] – which is not surprising, given the lack of accurate epidemiological evidence regarding their rate of malignant transformation. If clinical suspicion exists, the prophylactic removal of a small congenital nevus can be carried out usually fairly easily.

For medium-sized congenital nevi, the risk of malignant transformation is probably significant, but has not been precisely estimated [52]. However, medium-sized nevi are technically difficult to remove because of their size, and when they are removed they can leave a large and cosmetically unacceptable scar. The logical consequence of this dilemma is that this type of congenital nevus is often managed by regular visits to the doctor, supplemented by instructions being given to parents or to patients to check the lesion frequently, supplemented by photography and measurements to use as a baseline for future examinations.

The management of giant melanocytic nevi poses many difficulties, and the timing of surgery, if contemplated, may be important. Some authors suggest neonatal curettage [58]. The curettage must be carried out during the first month of life, when it is easy to identify the cleavage plane between the nevus and the normal tissue below. However, it is difficult to achieve histological clearance of the nevus, and a risk of malignant transformation still persists. Some authors have suggested that it is easier to identify malignant transformation after curettage than after conventional surgery, because new pigmented lesions are easier to visualize on “normal” skin after curettage [59].

Unfortunately, while there is an increased risk of melanoma in people with large congenital nevi, there is currently no scientific evidence that traditional surgical intervention reduces the risk of melanoma [60]. The cosmetic effects of extensive surgery and grafting for giant melanocytic nevi in early life can be disappointing and

may be complicated by painful scars, through which deeper melanocytic nevi may emerge after many years.

The presence of a larger congenital nevus, often on the upper side of the trunk and the head and associated with leptomeningeal melanocytosis, is a contraindication to surgical removal of the lesion, as the risk of melanoma persists in these areas [4].

### **How should a patient with multiple melanocytic nevi be managed?**

There is a close correlation between the number of melanocytic nevi and the risk of melanoma; according to one of the numerous case–control studies reported in the literature, the OR of melanoma associated with more than 45 nevi is 9.7 (95% CI, 5.4–17.4) [61]. There is, therefore, an argument that people with approximately 50 nevi should visit a dermatologist at least once a year for surveillance purposes [61]. The presence of atypical nevi, which are often present in people with numerous common nevi and phototype I or II, is another risk factor for melanoma that may require regular surveillance [10].

One approach is to teach such patients how to carry out self-examination of the skin. Self-examination allows features such as changes in shape and color to be identified at an early stage. One multicenter Italian survey of melanoma cases suggested that this procedure was associated with a reduction in the risk of late diagnosis of melanoma (thickness >1 mm), even after adjustment for confounding factors such as sex, age, and anatomic area of the lesion (OR, 0.70; 95% CI, 0.50–0.97) [11]. Berwick *et al.* conducted a case–control study to investigate the relationship between SSE and a reduced risk of fatal melanoma. They found that self-examination is associated with a reduced risk of melanoma incidence (OR, 0.66; 95% CI, 0.44–0.99) and with a possible reduced risk of advanced disease among melanoma patients (unadjusted risk ratio, 0.58; 95% CI, 0.31–1.11) [62].

There is no good evidence to suggest that trauma to benign nevi will increase the risk of malignant transformation. Moreover, stratification of nevi on the basis of their risk of transformation is not currently possible. Indeed, there is no good evidence that nevi that have an “atypical” appearance from a clinical point of view should be considered precursors of melanoma. Some clinically atypical nevi can show histological atypia (otherwise known as “dysplastic nevi”). However, even banal nevi can show histological atypia, since the correlation between clinical and histological atypia in nevi is poor [63].

The approach known as the “mole-mapping technique” – that is, recording images of all melanocytic lesions on the body and subsequently following them up to identify early possible malignant change – is a controversial procedure [17,18]. It is probably useful for periodic follow-up of people who are at high risk of melanoma. There is no evidence of any benefit of this technique in other situations, in comparison with examining the patient without analyzing the baseline characteristics of all the nevi.

## **Skin self-examination**

### **How commonly is skin self-examination done and what factors predict regular skin self-examination?**

Since SSE may be useful in reducing the rate of late presentation of melanoma [11], it is possible that promoting SSE in the general population might reduce the overall mortality from melanoma. The

American Cancer Society recommends a monthly SSE, a clinical skin examination every 3 years for those over the age of 20, and a clinical examination every year for those over the age of 40.

Little is known about how many people currently perform SSE. In an Australian study, SSE within the previous 12 months was reported by more than 25% of healthy people contacted by means of a telephone interview [64].

In a study in Connecticut, SSE was noted in 13.2% of melanoma patients and in 17.5% of controls [62]. In an Italian study, 40.5% of people visiting a pigmented-lesion clinic reported that they performed SSE [65]. The higher rates of SSE in the latter study are probably explained by the fact that the participants were examined at a specialized pigmented-lesion clinic aimed at providing melanoma screening and follow-up for those at increased risk of melanoma.

An important point is the frequency of SSE. In a random survey of the adult population in Rhode Island, USA, Weinstock *et al.* found that only 9% of recalled individuals performed a thorough skin examination at least once every few months [66]. Oliveria *et al.* found that 6.0% of men and 7.0% of women performed “rigorous” SSEs [14].

It is important to identify which factors increase the likelihood of an individual performing SSE, as it may help in refining educational strategies for melanoma prevention. Oliveria *et al.* found that skin awareness was a strong factor associated with SSE for both women and men (OR, 4.65 in men; 95% CI, 2.11–11.46; OR, 2.53 in women; 95% CI, 0.91–8.31). For women, variables significantly associated with SSE included previous benign biopsy or the presence of an abnormal mole (OR, 4.22; 95% CI, 1.72–12.01). In men, a family history of cancer (OR, 2.02; 95% CI, 1.02–4.13), physician examination (OR, 3.44; 95% CI, 1.77–6.94), and a change in diet to reduce the cancer risk (OR, 2.17; 95% CI, 1.12–4.23) increased the likelihood of SSE [14]. The Italian study used a multivariate model that adjusted for eye color, phototype, large numbers of common and atypical melanocytic nevi, sunscreen use, and having had a previous examination and having received a leaflet explaining SSE. The study found that, in men, the only variable significantly associated with SSE was a report of having received a leaflet explaining SSE (OR, 3.02; 95% CI, 1.24–7.38). For women, it was a report of having already had a previous consultation at a pigmented-lesion clinic (OR, 4.84; 95% CI, 1.57–14.93); the latter may be secondary to the explanations and advice about skin cancer prevention usually provided at a previous visit [65].

Weinstock *et al.* [15] evaluated the impact of participation in a mole-mapping program on the performance of thorough SSE. They found that 45% of those who were not performing SSE before participation reported performing it after receiving their images. However, 30% had never used the images to assist them in the self-examination. This study has important limitations: there was a small number of participants and the sample chosen only included a high-risk population.

### How accurate is skin self-examination?

In a cohort study of people at high risk of melanoma, Feit *et al.* showed that 32% of the malignancies were diagnosed because patients reported concern about the lesions – suggesting that patients were competent in identifying suspicious lesions using SSE [16].

Other papers confirm that most melanomas are discovered by the patient: 42–47% of men and 59–69% of women with melanomas reported that their melanomas were self-detected [17,67,68].

In a recent population-based study including 3772 Queensland residents with melanoma, McPherson *et al.* [18] found that 44.0% of the patients reported first noticing the melanoma themselves, whereas 25.3% of the melanomas were first noticed by a doctor, 18.6% by partners, and 12.1% by other laypersons (including other relatives, friends, and service people). In comparison with men, a greater proportion of women detected their melanomas themselves (57.1% vs 33.8%), whereas men had a greater proportion of partner-detected melanomas (26.7% vs 8.1%). Most commonly, the signs and symptoms reported by patients who are later found to have melanoma are changes in the color, size, or shape of a lesion, or an irritation or itch; they also report that the lesion looked different from other spots [18].

The sensitivity of SSE for certain risk factors for melanoma was studied by Gruber *et al.* [69]. They identified freckles, palpable nevi, and large nevi as potential risk factors for the development of cutaneous malignant melanoma. The sensitivity of self-reporting of the number of freckles on the right forearm was found to be 88%. The sensitivity was 63% for detecting one or more palpable arm nevi and 68% for detecting one nevus larger than 5 mm in diameter on the entire body.

Muhn *et al.* [70] studied the sensitivity of detecting an artificial increase in the size (0, 2, or 4 mm in diameter) of a preexistent nevus on the back using SSE. The patients examined their backs with a mirror before and after the manipulation of the mole. At this point, the patient was asked to determine which mole, if any, had been changed. They found that the sensitivity for detecting a 2 mm change was approximately 58% (95% CI, 49–68%). The sensitivity for detecting a 4 mm change was approximately 75% (95% CI, 66–83%). The specificity of the test (i.e., the ability to detect no change) was approximately 62% (95% CI, 53–72%). These results relate to a difficult area for body examination (on the back) and are thus likely to represent the worst-case scenario for the sensitivity and specificity of SSE for detecting changes in the size of a nevus, although this group of patients were highly selected and motivated. Another limitation of this study is that it only assessed changes in the size of the nevus, whereas it is a combination of changes in shape, thickness, and color, as well as the development of new moles, that allows patients to detect a malignant lesion.

A recent study by Oliveria *et al.* [71] investigated the sensitivity and specificity of SSE for detecting new and changing moles with or without the aid of baseline digital photographs in patients with dysplastic nevi. They found that the sensitivity and specificity of SSE for detecting both new and altered moles without photography were 60.2% and 96.2%, respectively, whereas SSE with photography showed significant improvements in diagnostic accuracy, with a sensitivity and specificity of 72.4% and 98.4%, respectively.

Weinstock and co-workers [72] tested the ability to detect an additional 5 mm pigmented lesion on the back. To improve the accuracy of SSE, they required half of the participants to complete a mole-mapping diagram (intervention group). They found that 33% of the control group and 52% of the intervention group ( $P = 0.06$ ) gave accurate assessments. Participants in the intervention group were better able to identify the added lesion or lesions ( $P = 0.01$ ).

SSE is associated with a reduced incidence of advanced melanoma, but it is prone to error in detecting early melanoma changes. Improving the accuracy of SSE may therefore be important in allowing detection of melanoma at an earlier stage and thereby reducing the mortality.



## Key points

- Nevus density is related to sun exposure and genetic factors.
- Dermoscopy improves the diagnostic accuracy for nearly all pigmented skin lesions in comparison with naked-eye examination and may reduce the rate of unnecessary biopsies when used for melanoma screening.
- Nevi may be surgically removed because of discomfort or appearance, or to exclude melanoma or prevent melanoma from occurring.
- There is a link between an increased number of melanocytic nevi and the risk of subsequent malignant melanoma.
- The rate of malignant degeneration of small congenital nevi (<1.5 cm) is unknown and is difficult to estimate because of their similarity to acquired melanocytic nevi.
- Congenital nevi with a diameter >20 cm have an approximately 4% risk of melanoma developing.
- Clinically, atypical nevi are a risk factor for melanoma.
- Removal of giant melanocytic nevi may not be associated with a reduced risk of melanomas, which may appear in noncutaneous sites, and surgical procedures such as grafting are often complicated by scarring and subsequent breakthrough pigmentation.
- Self-examination in people with large numbers of moles probably reduces the risk of late diagnosis of melanoma (thickness >1 mm).
- Approximately 50% of the population probably detect their own melanomas – women more frequently than men.

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## SECTION 3 Infective skin diseases, exanthems, and infestations

Masutaka Furue and Yuping Ran, editors

### CHAPTER 38

## Local treatments for cutaneous warts

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### Background

#### Definition

Cutaneous warts are extremely common, benign, and usually self-limiting. Infection of epidermal cells with the human papilloma virus (HPV) results in cell proliferation and a thickened, warty papule on the skin. The most common sites involved are hands and feet, though any area of skin can also be infected. Genital warts are also common and frequently sexually transmitted, but are not discussed in this chapter.

#### Prevalence

There are few reliable, population-based data on the prevalence of cutaneous warts. The prevalence rate varies according to different ages, populations, and periods of time, and it is the highest in children and young adults. Two large population-based studies revealed prevalence rates of 0.84% and 12.9% [1,2]. Studies in school populations showed rates of 12% in 4–6-year-olds and 24% in 16–18-year-olds [3,4].

#### Etiology and risk factors

Warts are caused by HPV, of which there are over 70 different types. Lesions are most common at sites of trauma, and probably result from inoculation of virus into minimally damaged areas of epithelium. Plantar warts are often acquired from common bare-foot areas; severe hand warts showed an occupational risk in butchers and meat handlers [5,6].

#### Prognosis

Non-genital warts in immunocompetent people are harmless and usually resolve spontaneously as a result of natural immunity within months or years. The rate of resolution is highly variable and probably depends on a number of factors, including host immunity, age, HPV type, and site of infection. One frequently cited study of an institutionalized population showed that two-thirds of warts resolved within a 2-year period [7]. Evaluation of clearance rates in

control groups in randomized controlled trials (RCTs) may also give some indication of natural clearance tendency, although a non-specific benefit of vehicle bases may make interpretation difficult. Twenty-three RCTs discussed in this chapter showed an average cure rate of 18% (range 0–73%) with placebo preparations after an average period of 10 weeks (range 4–24 weeks).

#### Diagnostic tests

Warts are frequently diagnosed clinically. Microscopic examination obtained surgically can confirm the diagnosis if there is doubt. HPV typing is used in research laboratories and occasionally in medico-legal cases to investigate child abuse.

#### Aims of treatment

To clear warts completely and permanently.

#### Relevant outcomes

- Cure rate (total clearance rate);
- recurrence;
- adverse reactions, such as pain and blistering.

#### Methods of search

##### Data sources and search strategy

All RCTs on the topical treatments for extragenital warts were identified, without limitation of language or publication status. The Medline, Embase, Cochrane Library, the Meta Register of Controlled Trials, CBM, and CNKI were searched. Reference lists of prior reviews, systematic reviews, and trials were also checked. The most recent searches were completed in June 2012.

#### Study selection and data extraction

Two investigators independently screened studies for inclusion, retrieved potentially relevant studies, and determined eligible studies. Disagreements were resolved by consensus. Two investigators independently extracted data from the included studies using

custom-made standardized forms and a third investigator was assigned with the checking process.

### Quality assessment

The criteria recommended by the *Cochrane Collaboration Handbook* were used to assess the methodological quality of included trials. It mainly focused on description of randomization (sequence generation progress), allocation concealment, blinding, addressing of incomplete outcome data, reporting of selective outcome, and other potential threats to validity [8]. The judgment for each entry was based on the answer of a question, with “yes” indicating “low risk of bias,” “no” indicating “high risk of bias,” and “unclear” indicating “either lack of information or uncertainty over the potential for bias” [8]. Disagreements were resolved by group consensus.

### Outcomes measurement

The primary outcome is the cure rate (total clearance rate). The secondary outcome is adverse reactions.

### Statistical analysis

All statistical analyses were performed using the duplicate data entry facility of Revman 5.0.25 (evidence-based medicine software) by two investigators [9]. In addition to 95% confidence intervals (CIs), relative risks (RRs) and mean differences (MDs) were respectively used for dichotomous and continuous outcomes. The  $\chi^2$  (chi-square test) statistic was calculated to determine the proportion of between-study variation due to heterogeneity. The value ranged from 0 to 100%, and high values indicated strong heterogeneity. If heterogeneity was low ( $P > 0.1$ ,  $\chi^2 < 50\%$ ), a fixed-effect model was used, otherwise a random-effect model was used. Intention to treat (ITT) was done for efficacy evaluation, and per-protocol (PP) analysis was done for adverse reaction evaluation.

## Results

### Salicylic acid or topical products containing salicylic acid

#### Efficacy

##### *Salicylic acid versus placebo*

Five RCTs [10–14] compared salicylic acid (SA) with placebo. SA preparations gave a higher cure rate of 73% versus that of 48% with placebo. The RR was 1.60, 95% CI was 1.16–2.23, number needed to treat (NNT) was 4 (95% CI, 3–7).

##### *Salicylic acid versus cryotherapy*

Three RCTs [15–17] compared SA with cryotherapy. The cure rates were respectively 60% and 70% in the two groups, and no significant difference was seen between the two treatments (RR, 0.85; 95% CI, 0.59–1.21).

#### Other comparisons

Seven RCTs [15,18–21] compared different products containing SA or compared SA with other topical treatments, such as glutaraldehyde and dithranol. The heterogeneous trials showed no convincing advantage of any particular delivery system for SA.

### Drawbacks

Generally, topical SA was reported to have no significant harmful effects. In one RCT that compared a mixture of monochloroacetic acid and 60% SA with placebo [13], one of the 29 patients in the

active treatment group developed cellulitis. Minor skin irritation was noted occasionally in some trials.

### Comments

There is reservation about the validity of pooled data from the different RCTs, because of the generally low quality of trials and the heterogeneity of their design and methodology. For instance, the RCTs included used different topical SA products, or some RCTs included patients with refractory warts whereas others excluded them. Despite this, we consider that there is good evidence for a modest benefit of SA in treating non-genital warts.

### Cryotherapy with liquid nitrogen

#### Efficacy

##### *Cryotherapy versus placebo or no treatment*

Two small RCTs compared cryotherapy with either placebo cream [22] or no treatment [23]. One of the two trials [22] reported a very low cure rate for cryotherapy (one of 11), while the other trial [23] showed a high cure rate in the placebo group (eight of 20). The pooled data of cure rates did not demonstrate a significant difference between the cryotherapy group and control group: 35% versus 34% (RR, 0.88; 95% CI, 0.26–2.95).

##### *Cryotherapy versus salicylic acid*

Three RCTs [15–17] compared SA with cryotherapy. The results have already been mentioned in the section entitled “Salicylic acid versus cryotherapy.”

##### *Cryotherapy versus bleomycin*

Two RCTs compared cryotherapy with intralesional bleomycin [24,25]. Because of heterogeneity of methodology and design, the two trials are described separately. One trial [24], which used 1 mg/mL bleomycin, obtained cure rates of 76.5% in the cryotherapy group and 94.9% in the bleomycin group (RR, 0.18; 95% CI, 0.03–0.90,  $P = 0.04$ ). Another RCT [25], using 0.5 mg/mL bleomycin, had a cure rate of 68.2% in the cryotherapy group and 100% in the bleomycin group (RR, 1.27 ( $1 < \text{RR} < 1.6$ );  $P < 0.05$ ).

#### Length of freeze

Four RCTs [26–29] compared aggressive and gentle cryotherapy in 592 adults and children. However, the definitions of “aggressive” and “gentle” used differed, and some studies included refractory warts whereas others did not. Overall, cure rates were 52% with aggressive cryotherapy and 31% with gentle cryotherapy (RR, 1.90; 95% CI, 1.15–3.15; NNT, 5; 95% CI, 3–7).

#### Interval between freezes

Three RCTs [15,30,31] showed no significant difference in cure rates among 2-week, 3-week, and 4-week intervals. Cure was generally achieved more quickly with shorter treatment intervals.

#### Optimum number of freezes

Only one RCT [32] examined this question in 115 adults and children who did not cure 3 months after 3-weekly cryotherapy and showed no benefit of prolonging cryotherapy for a further 3 months. The cure rates were 43% and 38% in the treated and untreated groups, respectively (no data available for calculating the odds ratio).

### Drawbacks

Only two RCTs included precise data on adverse events. Pain or blistering was reported by 64 of 100 participants (64%) treated with an “aggressive” (10 s) regimen, in comparison with 44 of 100

participants (44%) treated with a “gentle” (brief freeze) regimen (RR, 1.45; 95% CI, 1.12–2.31). Five participants withdrew from the aggressive-regimen group and one from the gentle-regimen group because of pain and blistering [26]. Pain or blistering was reported in 29%, 7%, and 0% of those treated at 1-week, 2-week, and 3-week intervals, respectively (no data available for the odds ratio) [30]. The rate of reported adverse affects was relatively high with a shorter interval, but this is likely to be a reporting artifact, as these participants were seen sooner after each treatment.

### Comments

The evidence from the available RCTs of cryotherapy for warts is limited and contradictory. Just as the RCTs on topical SA, the heterogeneities of study designs, methods, and populations make it difficult to draw firm conclusions from the pooled data. For instance, some trials included all types of warts on the hands and feet in all age groups, whereas others were more selective and simply focused on hand warts, or excluded certain groups such as those with mosaic plantar warts or refractory warts. Of particular note is the likelihood that the “populations” in these studies may have very different characteristics at different periods of time. For example, studies conducted in the 1970s in the UK would have included a higher proportion of participants with incident warts, which have a greater chance of cure or spontaneous resolution. In the 1980s and 1990s, more people with warts were treated in primary care. Thus, clinics would have had a more selected population with a higher proportion of refractory warts and correspondingly lower cure rates.

### Occlusive treatment with duct tape

#### Efficacy

##### *Duct tape versus placebo*

Two published trials did this comparison and did not show good cure rates with duct tape [33,34]. The trial by De Haen *et al.* [33] included 103 primary-school children who were randomly assigned to continuous duct tape and a no occlusive corn pad once a week. After 6 weeks, recurrence occurred in eight of 51 (16%) versus three of 52 (6%) of the trial warts. Curiously, other untreated warts resolved in 21% and 27% of the children, respectively. Wenner *et al.* [34] conducted a trial comparing occlusive duct tape (obscured by a sticky-backed fabric called moleskin) with the moleskin alone in 90 adult patients (the trial population had an unusually high age of 54 years). After 8 weeks, relapse occurred in eight of 39 (21%) versus nine of 41 (22%), respectively. Among the cured patients, six of eight (75%) and three of 10 (30%), respectively, had relapsed again after 6 months.

##### *Duct tape versus cryotherapy*

One trial compared occlusive treatment with duct tape and cryotherapy in 61 children and young adults [35]. The duct tape was applied for 6.5 days every 7 days, cryotherapy was given for 10 s every 2–3 weeks up to a maximum of six times. The cure rates were 22 of 30 (71%) and 15 of 31 (46%), respectively (RR, 1.52; 95% CI, 0.99–2.31). There were limitations to the trial: the number of patients was relatively small, 10 s of cryotherapy was inadequate, an unspecified number of outcome assessments were carried out over the phone, and it was not entirely clear how long after the treatment period was done.

### Drawbacks

Duct tape is simple, safe, and cheap. No significant adverse events were mentioned in any of these trials.

### Comments

None of these three trials are strong methodologically; thus, the results are somewhat contradictory and difficult to summarize meaningfully.

### Contact immunotherapy with dinitrochlorobenzene

#### Efficacy

Two small RCTs [22,36] of dinitrochlorobenzene (DNCB) in 80 children and adults achieved a cure rate of 80% (32/40) in comparison with 38% (15/40) in the placebo/no treatment groups (RR, 2.12; 95% CI, 1.38–3.26; NNT, 2; 95% CI, 2–4).

### Drawbacks

One trial [36] commented that six of 20 participants treated with 2% DNCB were sensitized only after the second application. All of them subsequently experienced significant local irritation, with blistering, when they were treated with 1% DNCB. None withdrew from the study.

### Comments

DNCB, a potent contact allergen, can cause significant local irritation and dermatitis, which probably precludes its use outside specialist centers.

### Photodynamic therapy

#### Efficacy

##### *Photodynamic therapy versus placebo*

One trial [37] randomized active (proflavine+black light) and placebo (picric acid + black light) treatments for recalcitrant symmetrical verrucae vulgaris, on the left and right sides of the body. The result showed no significant difference. Three trials [38–40] compared 5-aminolevulinic acid (ALA)-photodynamic therapy (PDT) with placebo-PDT, and all patients locally used keratolytic. Meta-analysis showed no significant difference (RR, 1.53; 95% CI, 0.86–2.73).

##### *Photodynamic therapy versus salicylic acid*

One RCT [41] including 120 adults and children compared methylene blue/dimethyl sulfoxide PDT with a mixture of SA and creosote. The cure rates were 8% and 15%, respectively.

##### *Photodynamic therapy versus cryotherapy*

In one RCT [42], four different types of light source for PDT were compared with cryotherapy. Topical SA was used for all patients. More warts were completely healed after white light-PDT than after red/blue light-PDT and cryotherapy.

##### *5-Aminolevulinic acid-photodynamic therapy versus high-frequency electrocautery*

One RCT [43] including 60 patients with plantar warts did this comparison. The cure rates of ALA treatment group were 37.5% (12 of 32 patients) and 17.86% (five of 28 warts), which were higher than those of the high-frequency electrocautery treatment group.

##### *5-Aminolevulinic acid-photodynamic therapy+salicylic acid versus microwave therapy*

One trial [44] including 126 plantar warts patients showed the cure rates were similar between two groups, while the recurrence rate was lower in the ALA treatment group than that in the microwave treatment group.



### **5-Aminolevulinic acid–photodynamic therapy versus semiconductor laser**

One RCT [45] reported that ALA–PDT is superior to semiconductor laser (cure rates 25/28 vs 18/28).

### **Methyl aminolevulinate–photodynamic therapy+chemical keratolytic treatment versus chemical keratolytic treatment**

One trial [46] evaluated methyl aminolevulinate (MAL)–PDT with or without chemical keratolytic treatment for hand warts in a population of renal transplant patients. The number of vanished warts showed no significant difference between two treatments.

### **5-Aminolevulinic acid–photodynamic therapy+CO<sub>2</sub> laser versus CO<sub>2</sub> laser**

In one trial [47], a total of 70 patients with plantar warts were randomly divided into two groups. The cure rates were 48.6% (17 of 35 patients) and 20% (seven of 35 warts) in ALA–PDT+CO<sub>2</sub> laser treatment group, higher than those of CO<sub>2</sub> laser treatment group.

### **Side effects**

One RCT [48] focused on the pain induced by PDT of warts, by filling in questionnaires about pain immediately and 24 h after each treatment. Forty-five patients were enrolled in a randomized, placebo-controlled trial with six consecutive ALA- and placebo–PDT treatments for recalcitrant foot and hand warts. Severe or unbearable pain was reported from a median of 17% (6–31%) of the ALA-treated warts and from a median of 2% (0–15%) from the placebo-treated warts immediately after the treatments. With increasing treatments, no significant change in pain intensity was observed, no significant relation was found between the pain intensity and the relative change in wart area. The pain was primarily characterized as burning and shooting. The pain lasted about 30 h (range: 1–96 h).

Nine RCTs [38–40,42–47] reported the side effects during or after the PDT treatment. Pain, burning, itching, local anesthesia, swelling, and erythema were common; most were mild/moderate and acceptable. No treatments were suspended because of pain.

### **Comments**

The fact that most trials used different protocols of PDT (different photosensitizer, different light sources, different treatment intervals, and so on) makes it difficult to draw a definite conclusion. So far, PDT appears to offer no particular advantages in cure rates or adverse effects than other simpler and cheaper local treatments available. But for recalcitrant warts, it might be an alternative approach, which should be proved by further research.

## **Intralesional bleomycin**

### **Efficacy**

#### **Bleomycin versus placebo**

Conflicting results were reported in five RCTs of intralesional bleomycin. Three trials [49–51] reported higher cure rates with bleomycin than with placebo, one [52] showed that placebo was associated with higher cure rates than bleomycin, and one [53] showed no significant differences between bleomycin and placebo. The pooled results showed that bleomycin was more effective than placebo in the treatment of cutaneous warts (RR, 3.84; 95% CI, 2.19–6.71).

#### **Bleomycin versus cryotherapy**

Two RCTs [24,25] compared liquid-nitrogen cryotherapy with intralesional bleomycin. The results were shown in the section “Cryotherapy with liquid nitrogen.”

### **Different concentrations of bleomycin**

One RCT [54] in 26 adults, comparing 0.25, 0.5, and 1.0 IU/mL bleomycin, showed cure rates of 73%, 88%, and 90% of warts, respectively; the differences were not statistically significant.

### **Drawbacks**

No precise data on adverse effects were provided in any of the RCTs. One RCT [52] reported “adverse events” in 19/62 (31%) participants, but the nature of the adverse events and the proportions in the active treatment and placebo groups were not specified. Three of the trials [49,50,54] reported that most participants experienced pain. In two trials [50,51], local anesthetic was used routinely before the injection of bleomycin. One trial [54] reported pain was seen in most participants, which was irrespective of dose. In one trial [49] of 24 participants who received bleomycin, two patients withdrew because of the pain of the injections and pain in the period after the injection.

### **Comments**

Again, methodological and statistical heterogeneity (different outcomes, trial periods, units of analysis, numbers of injections, vehicles, and concentrations) make it impossible to organize the data from these trials.

## **5-Fluorouracil**

### **Efficacy**

#### **5-Fluorouracil versus placebo**

One RCT [55] compared 5-fluorouracil with placebo. Altogether, 60 patients (including 40 children) were randomized to be treated with topical 5-fluorouracil for 4 weeks and placebo. During the procedure, 31 patients were lost to the active treatment and the cure rate was 60%, versus three lost to the placebo treatment and the cure rate was 17%. There were statistically significant difference between the two treatments (RR, 7.44; 95% CI, 2.86–19.35).

#### **5-Fluorouracil cryotherapy versus cryotherapy+placebo**

One RCT [56] compared cryotherapy combination with 5-fluorouracil and cryotherapy combination with placebo; the cure rates were 58.57% and 65.29% respectively. There was no significant difference (RR, 0.55; 95% CI, 0.22–1.40).

#### **5-Fluorouracil+duct tap versus duct tape**

One RCT [57], including 40 patients, treated with 5-fluorouracil combined with duct tape and duct tape alone for 12 weeks. The cure rates were 95% (19/20) and 10% (2/20) respectively (RR, 9.50; 95% CI, 2.54–35.51).

### **Drawbacks**

Only one trial [57] mentioned topical 5-fluorouracil side effects. Eleven cases of fingertip or periungual warts had nail separation after topical 5-fluorouracil treatment; the rate was 22.9% out of 48 cases in total. However, the nature and proportion of the side effects of the treatment were not elaborated.

### **Comments**

Methodological and statistical heterogeneity (different outcomes, trial periods, units of analysis, vehicles, and concentrations) make it impossible to organize the data from these trials.

## **Localized heat therapy**

### **Efficacy**

#### **Localized heat therapy versus placebo**

Two RCTs [58,59] compared localized heat therapy with placebo; because of heterogeneity in methodology and design, the two trials

are described separately. One trial [58] including 13 patients (29 warts) used local hyperthermia at 50°C lasting 30 min. The cure rates were 86% (25/29) in the treatment group and 41% (7/17) in the control group, the difference was statistically significant (RR, 8.93; 95% CI, 2.14–37.34). Another RCT [59] used local hyperthermia at 44° lasting 30 min once a day for three consecutive days. Two weeks later, patients received similar treatments for two consecutive days. Patients in the control group received a red spot on the targeted lesion without experiencing a heating sensation. Three months later, the cure rates were 53.57% (15/28) and 11.54% (3/26), respectively. The difference was statistically significant (RR, 8.85; 95% CI, 2.15–36.37).

### Drawbacks

One trial [59] showed that 80% of patients (12/15) in the treatment group who had initial complaints of load-bearing pain reported a decreased sensation of pain, one experienced an increased sensation of pain, and two remained stable. In the control group, 14.3% of patients (2/14) reported a decreased sensation of pain, five experienced an increased sensation of pain, and three remained stable. There was a significant difference between the two groups (RR, 24; 95% CI, 3.38–170.38).

### Comments

Methodological and statistical heterogeneity (different outcomes, trial periods, units of analysis, vehicles, and concentrations) make it impossible to organize the data from these trials.

## Light and laser treatment

### Efficacy

#### *Intense pulsed light*

In one trial [60], 79 patients with recalcitrant hand and foot warts were included and randomized into treatments with either paring of warts followed by intense pulsed light (IPL) or paring of warts alone. No significant difference in cure rate was found between the two intervention groups, but the pain intensity after paring plus IPL was significantly higher than that after paring alone.

#### *Pulsed dye laser*

One trial [61] compared the efficacy and safety of pulsed dye laser (PDL) (595 nm PDL + cooling pulses) with a placebo (cooling pulses alone) in the treatment of patients presenting palmoplantar warts. For both groups, hyperkeratosis was removed manually with a scalpel before each session. The results showed that 64% (48/75) of warts in the laser group resolved completely compared with 13% (4/30) in the placebo group ( $P < 0.001$ ). Three trials [62–65] (including adults and children) compared PDL therapy with cryotherapy and no superior efficacy was found (RR, 1.02; 95% CI, 0.85–1.21). One controlled study [66] included 66 lesions from 19 patients. PDL was applied to 33 lesions following 30% SA application twice a day for 5 days; the remaining 33 lesions underwent PDL therapy alone. PDL was administered in both groups at 4-week intervals varying from one to five sessions. Complete clearance was observed after 2.2 sessions in the SA+PDL group versus 3.1 sessions in the PDL group ( $P < 0.05$ ). Although the clearance rate showed no difference between the SA+PDL group and the PDL group after all the sessions, adding SA to PDL decreased the number of sessions to an extent.

#### *Q-switched laser*

Two trials [67,68] (including 212 adults and children with verruca planar) compared Q-switched laser therapy with cryotherapy. All

patients took transfer factor capsules; 92 patients were injected with immunoenhancement for 3 weeks. Q-switched laser therapy obtained higher cure rates (RR, 1.26; 95% CI, 1.12–1.43). The other two trials [69,70] compared Q-switched laser therapy with combination treatments (retinoic acid cream,  $\alpha$ -2b interferon (IFN) ointment, ceramic grinding treatment). The combination treatments were superior to single laser treatment.

#### *CO<sub>2</sub> laser*

Three trials [71–73] (including 453 adults) compared CO<sub>2</sub> laser therapy with cryotherapy. A significant difference was found between the two treatments (RR, 1.36; 95% CI, 1.01–1.83). Two trials [74,75] (including 575 adults) compared CO<sub>2</sub> laser therapy with microwaves therapy. CO<sub>2</sub> laser therapy did not give higher cure rates (RR, 1.05; 95% CI, 0.78–1.41). Another nine trials [64,72,76–82] compared topical treatments ( $\alpha$ -2b IFN ointment, semiconductor laser, different types of CO<sub>2</sub> laser, retinoic acid drugs, etc.) combined with or without CO<sub>2</sub> laser therapy. The results showed that combination treatments were superior to single laser treatment.

#### *Holmium laser*

One trial [83] including 120 children and adult patients with plantar warts compared holmium laser with cryotherapy. The cure rate was 97.5% (78/80) versus 55% (22/40). A significant difference was found between the two treatments, but high risk of bias was found in this trial.

### Drawbacks

Ten RCTs [60,63,65,66,69,76–80] reported the side effects caused by light or laser therapy, including pain, erythema, swelling, hyperpigmentation, burning, itching, desquamation, crusts, and scar. Most of them were mild and tolerable.

### Comments

PDL appears to be an effective treatment in non-genital cutaneous warts, but the efficacy seems to be no superior to that of traditional treatments (cryotherapy). Other laser treatments (Q-switched laser, CO<sub>2</sub> laser, etc.) seem to be more effective than cryotherapy, but more placebo-controlled trials should be undertaken to prove the results. The combination treatment could be considered in clinical practice.

## Imiquimod

### Efficacy

#### *Imiquimod versus retinoic acid drugs*

Four RCTs [84–87] (including 308 adults and children) did this comparison. Topical 5% imiquimod cream did not give higher cure rates (RR, 1.26; 95% CI, 0.98–1.63).

#### *Imiquimod+retinoic acid drugs versus retinoic acid drugs*

Three trials [84,88,89] (including 216 adults and children) did this comparison. The cure rate was 42.99% versus 24.04%. A significant difference was found between the two treatments (RR, 1.80; 95% CI, 1.20–2.70).

#### *Imiquimod+retinoic acid drugs versus imiquimod*

Three trials [84,90,91] (including 229 adults and children) did this comparison. The cure rate was 52.63% versus 22.61%. A significant difference was found between the two treatments (RR, 2.33; 95% CI, 1.59–3.42).

### Other comparisons

Nine trials [92–100] compared topical treatments ( $\alpha$ -2b IFN ointment, traditional Chinese medicine, cryotherapy, microwave, hot water immersion, etc.) with or without imiquimod cream. The limited evidence showed the combination treatments were superior to single treatment.

### Drawbacks

Sixteen RCTs reported the side effects caused by imiquimod cream, including erythema, burning, tingle, swelling, erosion, itching, edema, desquamation, and pigmentation. No systemic side effects were reported.

### Comments

No evidence showed good efficacy of 5% imiquimod cream on non-genital cutaneous warts. Although the pooled data showed combined treatment with retinoic acid drugs to be effective in verruca planar, the results should be verified by high-quality RCTs.

## Retinoic acid drugs

### Efficacy

#### Retinoic acid

*Retinoic acid versus  $\alpha$ -2b interferon* Two RCTs [101,102] (including 218 adults and children) compared retinoic acid ointment with  $\alpha$ -2b IFN ointment. Topical retinoic acid ointment did not give higher cure rates (RR, 0.87; 95% CI, 0.59–1.31).

*Retinoic acid+ $\alpha$ -2b interferon versus retinoic acid* Three RCTs [101–103] (including 324 adults and children) did this comparison. A significant difference was found between the two treatments (RR, 1.99; 95% CI, 1.53–2.57).

*Retinoic acid+ $\alpha$ -2b interferon versus  $\alpha$ -2b interferon* Four RCTs [101,102,104,105] compared retinoic acid cream combined with  $\alpha$ -2b IFN ointment in 350 adults and children. The pooled data showed a significant difference between the two treatments (RR, 1.84; 95% CI, 1.45–2.32).

#### Tazarotene

*Tazarotene+ $\alpha$ -2b interferon versus tazarotene* Two RCTs [106,107] did this comparison in 68 patients with verruca planar and 104 patients with plantar warts. The combination treatment group had a higher cure rate than the tazarotene ointment only group (RR, 2.79; 95% CI, 1.62–4.81).

*Tazarotene+ $\alpha$ -2b interferon versus  $\alpha$ -2b interferon* In one RCT [108], 98 adults and children with verruca planar were randomized into two groups (topical tazarotene cream combined with  $\alpha$ -2b IFN ointment group and topical  $\alpha$ -2b IFN ointment alone group). After 4 weeks, the cure rates were 48.08% (25/52) versus 23.91% (11/46). The former had greater efficacy than the latter on treatment of verruca planar.

*Tazarotene versus ftibamzone* Two RCTs [109,110] (including 347 adults and children with verruca planar) compared tazarotene cream with ftibamzone ointment. The pooled data did not demonstrate a significant difference in cure rates (RR, 1.15; 95% CI, 0.80–1.63).

### Other comparisons

Retinoic acid ointment, tazarotene cream, adapalene gel, and isotretinoin gel were respectively compared with different products

or topical treatments in 16 trials [91,97,111–124], seven trials [84,89,90,125–128], five trials [120,129–132], and one trial [133]. The limited evidence showed that the combination treatments were superior to the single treatment. However, all the trials had a high risk of bias, so the results were less worthy of belief.

### Drawbacks

All RCTs except one trial [120] reported the side effects caused by retinoic acid drugs. The most common drawbacks were erythema, itching, and desquamation. Most patients could get better after treatment cessation, using vitamin E ointment, reducing treatment frequency, or even keeping on treatment. Other side effects were burning, swelling, photosensitive, tight skin, tingling, pigmentation, and so on.

### Comments

It was hard to draw a definite conclusion on the efficacy of retinoic acid drugs because high-quality placebo-controlled trials were absent. Although the pooled data showed that retinoic acid drugs combined with  $\alpha$ -2b IFN treatment were effective in verruca planar, the generally low quality of trials means there are reservations. Furthermore, clinical heterogeneity made it impossible to organize the data from most trials. So there was no compelling evidence to give retinoic acid drugs to non-genital cutaneous warts patients.

## Other local treatments for warts

Intralesional IFN as a treatment for warts is more of historical interest. Six trials [134–139], most dating from the 1970s and 1980s, were found using this treatment; evidence provided by all the trials was severely limited by heterogeneity of the methodology and design, and overall did not suggest any striking efficacy.

In one RCT [140] of intralesional antigen therapy, a form of local immunotherapy was designed to elicit an immune reaction in warts, and patients were injected with *Candida*, *mumps*, or *Trichophyton* antigens. Unfortunately, the design of the trial was made more complex by the addition of intralesional IFN, resulting in four treatment arms (antigen with or without IFN and placebo with or without IFN) rather than two, which would have given much clearer data. Up to five injections were given at 3-weekly intervals into the largest wart in each patient. Blinding involved only the patients and not the investigators, introducing a source of potentially significant bias. The main outcome reported was a reduction of more than 75% in the wart surface area at the end of treatment – an outcome of no relevance to patients (who naturally want their warts cleared). No long-term follow-up appears to have been carried out. A total of 201 patients with refractory warts completed the trial; 57 of 95 patients (60%) injected with antigen with or without additional IFN experienced the resolution of at least one wart, in comparison with 25 of 106 patients (24%) injected with saline or IFN alone. The number of patients who experienced complete clearance of all warts is a little difficult to ascertain from the paper, but it appears to have been 21 of 95 (22%) in the treatment groups and 11 of 106 (10%) in the “placebo” groups. For a fairly painful and expensive treatment, this does not appear to offer any striking advantages.

One RCT [141] compared 20% zinc oxide and 15% SA complex, involving 44 patients who were randomized to the two treatments twice a day for 3 months. The results showed that the cure rates of zinc oxide and SA complex group were respectively 50% and 42%, and there was no statistically difference between the two treatments (RR, 1.44; 95% CI, 0.44–4.76). Topical zinc oxide is a possible treatment of warts, but needs more RCTs to support.



One RCT [142] compared topical  $\alpha$ -lactalbumin-oleic acid with placebo. The trial employed an unusual hybrid molecule (consisting of a combination of  $\alpha$ -lactalbumin from human breast milk and oleic acid), which was said to be lethal to a wide range of transformed cells but harmless to normal ones. The trial was properly randomized and double blinded, and the analysis focused on the main outcome of a more than 75% reduction in wart volume, rather than the more relevant complete clearance of warts. Unfortunately, the trial defaulted to an open-label design after 3 months, making the long-term follow-up data unconvincing. Although 100% of patients in the treatment group were reported to have experienced a reduction in wart volume of more than 75%, only 21% of the lesions in the treatment group resolved completely. Nine of 20 patients (45%) with active treatment experienced the resolution of at least one wart, in comparison with three of 20 (15%) in the placebo group (RR, 3.0; 95% CI, 0.95–9.48). Given the size of the trial, and consequently the wide CIs, the results were unconvincing.

One RCT [143] compared smoke from leaves of *Populus euphratica* Olivier and conventional cryotherapy, once a week, for 10 times. After 22 weeks, the cure rates were 68% (16/24) and 46% (13/28) respectively (RR, 2.31; 95% CI, 0.75–17.13).

No RCTs were identified that studied the efficacy of the following treatments: surgical excision, curettage and cautery, formaldehyde, podophyllin, and podophyllotoxin.

### Key points

- Topical preparations containing SA are generally effective and safe for treating warts.
- The available, rather limited, evidence shows that no significant difference was seen between cryotherapy and topical treatments containing SA.
- Contact immunotherapy with DNCB appears to be a promising treatment, but is probably best reserved for highly refractory warts.
- PDT and PDL therapy do not appear to have any particular advantage in terms of higher cure rates or fewer adverse effects than the other simpler and cheaper local treatments available.
- There is no compelling evidence for the efficacy of intralesional bleomycin.

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# Molluscum contagiosum

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## Background

### Definition

Molluscum contagiosum is a benign infection of the skin and mucous membranes caused by the molluscum contagiosum pox virus. Most people with mollusca have multiple lesions, which typically begin as small papules that enlarge to around 3–6 mm and rarely to more than 1 cm in diameter. Fully developed papules typically have a central umbilication or depression that contains a white, waxy, curd-like core. Most lesions resolve without scarring, but they may cause discomfort and/or itching (Figure 39.1) [1]. Mollusca can be associated with a surrounding dermatitis and occasionally a reactive skin eruption similar to Gianotti–Crosti syndrome [2].

### Incidence

Infections with the molluscum contagiosum virus occur throughout the world, but the incidence varies considerably, with higher rates in areas with warm climates [1]. Children are most often affected [3–5]. In a British study, the incidence was 243 per 100 000 person-years (py) in males and 231 per 100 000 py in females. Ninety percent of cases were reported in children aged 0–14 years (incidence 1265 per 100 000 py) [4]. In New Guinea, the annual attack rate was 6% in children aged 0–9 years [6]. Incidence rates are higher in American Indians and Alaska Natives than in the general US population [7]. Patients with weakened immune system are particularly prone to molluscum infection and have increased difficulty in clearing lesions (point prevalence in patients with human immunodeficiency virus/acquired immune deficiency syndrome (AIDS): 5–18%) [8–11]. A history of eczema was found in 62% of children with molluscum contagiosum in Australia [12]. Another Japanese study found that lifetime molluscum was increased in young children with atopic eczema [13].

### Etiology

Molluscum contagiosum, also known as *Molluscipoxvirus*, is a member of the pox virus (Poxviridae) family [14,15]. Transmission of molluscum occurs during contact with infected lesions, contami-

nated fomites, or sexual contact [16]. Autoinoculation through scratching is also suspected, especially as lesions can develop along scratchmarks (koebnerization) [17]. Outbreaks have occurred among children attending swimming pools [18,19].

### Prognosis

After a variable incubation period (2–6 months), the lesions usually persist for several months and resolve as a result of an inflammatory response which may develop spontaneously, following trauma (e.g., scratching) or secondary bacterial infection [1,20,21]. In immunocompromised people – for example, patients with AIDS – molluscum contagiosum usually does not resolve spontaneously and is often refractory to treatment [1,22].

### Aims of treatment

Molluscum contagiosum is self-limiting in immunocompetent individuals. Many parents of children with molluscum may seek treatment because of concerns about the appearance of the lesions, lesions becoming sore due to friction from clothing and in skin folds, persistence of lesions, spread of lesions, concern about secondary infection, or because of other people's comments. The aims of treatment are to shorten the duration of the condition, to resolve discomfort (e.g., itching), to limit spread, and to prevent secondary bacterial infection [1].

### Relevant outcomes

Clinical cure of all infected lesions is the clinically most relevant outcome. Treatment success is defined as the proportion of patients completely cleared of all molluscum contagiosum lesions. Treatment success should ideally be assessed 4–8 weeks after the discontinuation of treatment because of the tendency of molluscum to heal spontaneously in healthy children. Secondary outcomes include the time to clearance of all lesions and the cosmetic result.

### Methods of search

We included randomized controlled trials (RCTs) of all interventions for cutaneous, nongenital infection with molluscum contagiosum in immunocompetent patients. We updated the previous



Figure 39.1 Molluscum contagiosum.

edition's chapter by searching the Cochrane Controlled Trials Register (May 2013), the Cochrane Library for systematic reviews (May 2013), and Medline (June 2006–May 30, 2013).

## Question

**In immunocompetent patients with cutaneous, nongenital molluscum contagiosum, what is the efficacy (defined as the proportion of patients completely cleared of all lesions at 4–8 weeks after discontinuation of treatment) of physical destructive methods, topical and systemic treatments, or waiting for spontaneous resolution?**

### Evidence summary

A Cochrane review on the interventions for cutaneous molluscum contagiosum was published in 2006 and subsequently updated to include studies published up to June 2009 [23]. Only 11 studies, with a total number of 495 participants, could be analysed. Study limitations included no blinding (four studies), high drop-out rates (three studies), and no intention-to-treat analysis, and the small study sizes meant inadequate power to detect possible important differences. The overall conclusion from the authors was that no single intervention has been shown to be convincingly effective in the treatment of molluscum contagiosum [23].

We identified another seven relevant studies, including two of the largest RCTs ever conducted in the intervention of molluscum contagiosum. These two studies, identified by Katz and Swetman [24], suggest that imiquimod 5% is no more effective than placebo in achieving clearance of mollusca, yet these studies have never been published in a peer-reviewed journal [25]. A study by Mutairi *et al.* comparing 5% imiquimod cream with cryotherapy is the only

RCT we have identified that provides supporting evidence for a physical destructive method in the treatment of molluscum contagiosum [26]. The clearance rate of 100% (37 out of 37 subjects) was the highest out of all studies, though clearly tolerability and scarring are major drawbacks. This study also found a 92% (34/37) clearance rate with imiquimod after 16 weeks, in contrast to the previously discussed Papadopoulos studies [25], which found clearance rates of 24% (112/470 – pooled data) after 18 weeks.

Cantharidin, a blister beetle extract, has been widely used to treat viral warts as well as molluscum contagiosum. However, the only RCT we found for the treatment of mollusca suggests that there was no significant improvement compared with placebo, though it was a small study that may have been underpowered [27].

Despite previous studies suggesting no benefit in treating mollusca with potassium hydroxide compared with placebo [28, 29], there have been two further studies published, by Rajouria *et al.* [30] and Uçmak *et al.* [31], showing a greater reduction in mean lesion count and improved complete clearance with potassium hydroxide. However, in both studies, patient numbers were small and no control groups were present.

## Sodium nitrite

### Efficacy

After 3 months of treatment with sodium nitrite 5%–salicylic acid 5% cream with occlusion on each lesion overnight, 75% of patients (12/16) completely cleared, in comparison with 25% of children (4/16) treated with salicylic acid 5% cream [32].

### Drawbacks

Brown staining of the skin was recorded in six patients out of 16 with active treatment, but in none in the control group. The treatment is awkward and time consuming, and causes irritation in some patients (frequency not reported) [32].

### Comment

Because of potential staining, sodium nitrite is not recommended for facial molluscum contagiosum. It appears to be beneficial for lesions on the trunk, although larger trials are needed to confirm the results.

## Salicylic acid, phenol

### Efficacy

Salicylic acid 12%, lactic acid 4% gel (Salatac) applied once to twice weekly, and 10% phenol in a 70% alcohol solution applied once daily had similar clearance rates to those of the vehicle (Salatac 57% (21/37) versus phenol 42% (17/41) versus placebo 44% (16/36); completely cleared,  $P = 0.38$ ) [33].

### Drawbacks

Significantly more patients discontinued treatment due to stinging in the salicylic acid group in comparison with phenol and vehicle. No serious adverse events occurred [33].

### Comment

Because an efficacy greater than that of the vehicle was not demonstrated in this study, neither salicylic acid nor phenol are recommended. The sample size of the study was quite small, and important treatment differences might have been missed. In contrast to the full-text paper, in which the results were based on an intention-to-treat analysis, the authors reported results after excluding drop-outs in a previously published abstract. Salicylic acid appears to be ben-



eficial in the per-protocol analysis, highlighting the potential of misleading inferences due to inappropriate statistical methods [33,34].

### Imiquimod versus vehicle and cryotherapy

#### Efficacy

Theos *et al.* found imiquimod 5% cream applied three times a week for 12 weeks was not superior to the vehicle in inducing complete clearance (imiquimod 33.3% completely cleared (4/12) versus vehicle 9.1% (1/12);  $P = 0.32$ ); partial responses (defined as at least a 30% reduction in the lesion count) were more frequent in patients treated with imiquimod [35]. An RCT by Al Mutairi *et al.* demonstrated imiquimod 5% cream applied five times a week led to complete cure at 16 weeks in 34/37 participants (22/37 at week 6), compared with complete clearance in all 37 patients receiving once-weekly cryotherapy after 3 weeks [26]. Interestingly, a commentary by Katz and Swetman [24] in 2013 on the deficiencies of US law in failing to mandate that important negative studies are published in full in peer-reviewed journals highlighted two unpublished RCTs (by Papadopoulos in 2006) conducted in comparing imiquimod 5% used three times weekly for up to 16 weeks against placebo [25]. Both studies found no statistical difference in complete clearance rates of those treated with imiquimod, 52/217 and 60/253 (both 24%) compared with placebo, 60/253 and 35/216 (24% and 16%).

#### Drawbacks

Tolerability did not differ significantly between imiquimod and the vehicle in the study by Theos *et al.* with local skin reactions and pruritus commonly reported in both groups [35]. The Al Mutairi *et al.* study showed significantly more adverse effects with cryotherapy compared with imiquimod, including blistering (9/37), pigmentary changes (15/37), and scarring (8/37). Together with the treatment-associated pain of cryotherapy, this represents a major drawback of the use of this modality in young children. Pain during application (27/37) and erythema (28/37) were also common side effects reported with imiquimod [26]. A pharmacokinetic study suggested that percutaneous absorption in imiquimod was low; however, leukopenia and neutropenia were commonly noted [36].

#### Comment

With a total of 23 participants included, the first study was not sufficiently powered to show small differences [35]. The Al Mutairi *et al.* study reported high clearance at 16 weeks, for both imiquimod and cryotherapy, but given the self-limiting nature of molluscum, the lack of a placebo arm in this trial was a significant flaw, as was the lack of description of method of randomization and subsequent allocation concealment and blinding. The unpublished trials cited by Katz and Swetman highlight the problem of publication bias against studies with negative results. The original manufacturer of imiquimod and clinicians involved in their pivotal studies chose not to publish the results of these studies in a journal, yet they are available on the US Foods and Drugs Administration (FDA) website. As a result, these key studies have not been picked up and included in dermatology textbooks, reference guides, and even the Cochrane review on the interventions for cutaneous molluscum contagiosum.

### Australian lemon myrtle (*Backhousia citriodora*)

#### Efficacy

The essential oil of the Australian lemon myrtle (*Backhousia citriodora*) (Herbal BioScience, Oakvale, California, USA), applied once

daily for 21 days, induced partial remission (defined as at least a 90% reduction in the lesion count) in 56% (9/16) of patients, in comparison with 0% (0/15) treated with the vehicle. Complete response rates are not reported [37].

#### Drawbacks

None. The treatment was well tolerated in the study [37].

#### Comment

Australian lemon myrtle appears to be beneficial against molluscum contagiosum. However, complete response rates are not reported, and complete clearance is probably of most relevance for the patient [37]. Further evidence has suggested cytotoxic effects associated with the use of this oil [38,39], which has led the research group (Centre for Biomedical Research Inc.) to evaluate another formulation of lemon myrtle to improve safety and efficacy [40].

### Combination of essential oil of *Melaleuca alternifolia* with iodine

#### Efficacy

The same company that evaluated *Backhousia citriodora* went on to test another essential plant oil obtained from *Melaleuca alternifolia*, more widely known as tea tree oil. They compared melaleuca oil against melaleuca plus iodine versus iodine alone in a three-armed RCT of 53 children and found that 16 out of 19 children (84%) had a greater than 90% reduction of lesions in the combination group, compared with one out of 16 (6%) and three out of 18 (17%) for the iodine and melaleuca-only groups ( $P < 0.01$ ) by the end of day 30 using an intention-to-treat analysis [40]. Complete response rates are not reported.

#### Drawbacks

Adverse effects were limited to application site redness that did not result in any children withdrawing from the study. Long-term scarring after resolution of the lesions was not assessed.

#### Comment

This study suggests that a specially formulated combination of tea tree oil and iodine is more effective than either product used alone, although the absence of a vehicle-only group is a limitation given the tendency of molluscum to resolve spontaneously. The internal validity of this company-sponsored trial is questionable given that the method of randomization and subsequent allocation concealment is not described, and although parents and the evaluating physicians were reported to have been blinded to the treatment allocation, it is unclear whether assessment was truly blinded given that iodine stains the skin. Plant extracts could have a beneficial effect in inducing local clearance of mollusca, and an independent trial of tea tree oil plus iodine versus a vehicle of similar colour and smell with blinded assessment of complete clinical response might be worthwhile.

### Povidone iodine solution combined with salicylic acid plaster

#### Efficacy

Ohkuma found that 10% povidone iodine solution and 50% salicylic acid plaster was effective in curing 20/20 participants (100%) compared with 3/5 who received povidone iodine alone (60%) and 7/10 who received salicylic acid plaster alone (70%). Thus, the combination treatment cured more participants than either component alone (and more rapidly – 26 days, 86 days, and 47 days were mean

time to cure for each group respectively), though this failed to reach statistical significance [41].

### Drawbacks

All participants developed local redness within 3–7 days of starting treatment. The duration of redness was variable, and the more marked the inflammation the earlier the cure was [41].

### Comment

Based on the small number in the comparator groups and lack of statistical difference between the groups there is insufficient evidence to recommend this treatment.

## Benzoyl peroxide

### Efficacy

In total, 73% (11/15) of patients treated with benzoyl peroxide 10% cream twice daily for a total of 4 weeks had complete remission of all lesions at week 6, in comparison with 33% (5/15) of patients treated with tretinoin 0.05% cream (relative risk [RR], 2.20; 95% confidence interval [CI], 1.01–4.79;  $P = 0.05$ ) [42].

### Drawbacks

Side effects were limited to mild dermatitis in both treatment groups (exact numbers not reported) [42].

### Comment

Benzoyl peroxide 10% cream appears to be beneficial for molluscum contagiosum. However, owing to poor reporting quality and methodological shortcomings (i.e., failure to carry out an intention-to-treat analysis) bias cannot be ruled out [42], and better studies are needed.

## Cantharidin versus placebo

### Efficacy

Cantharidin is a topical vesicant that has been used to treat molluscum for several decades. It is an extraction from blister beetles, *Cantharis vesicatoria*, and when applied to the skin it produces a small intraepidermal blister that usually heals without scarring. In this randomized double-blind study, 15% (2/13) of those who received cantharidin and 6% (1/16) of those who received vehicle achieved complete clearance after 8 weeks, which was not statistically different [27].

### Drawbacks

Although the placebo vehicle had an identical texture and smell to the active drug, there were significant differences in reported adverse effects in that blistering was reported in 12/13 of those who received cantharidin, but in only 8/16 receiving placebo. The active group also experienced more pigmentary changes (6/13 vs 0/16). Three patients in the cantharidin group were excluded because they were later found not to meet the inclusion criteria [27].

### Comment

Despite anecdotal evidence supporting the use of cantharidin, this study is the first prospective, placebo-controlled, randomized trial evaluating the safety and efficacy of cantharidin for molluscum contagiosum. Although the performance of cantharidin was similar to that of placebo in this study, it was probably too small to be conclusive.

## Potassium hydroxide versus saline and tretinoin cream

### Efficacy

Bazza and Ryatt reported a study where treatments were randomized to the right or left side of the body. Application of 5% potassium hydroxide was compared with 0.9% saline. In both groups, 85% (17/20) of patients were cured at 12 weeks [28]. The same comparison was made by Short *et al.*, where treatment with 10% potassium hydroxide was successful after 3 months in 70% (7/10) compared with 20% (2/10) in the saline group [29]. Pooling these data showed no significant benefit from potassium hydroxide. Rajouria *et al.* compared 5% potassium hydroxide with tretinoin 0.05% cream in a nonrandomized controlled study, with 25 patients allocated to each treatment, and found at 4 weeks a mean reduction in lesion count from 9.48 ( $\pm 3.00$  standard deviation [SD]) to 1.67 ( $\pm 0.58$  SD) and from 8.35 ( $\pm 2.82$  SD) to 2.00 ( $\pm 1.00$  SD) for potassium hydroxide and tretinoin respectively [30]. A study by Uçmak *et al.* compared treatment with potassium hydroxide at concentrations of 2.5% and 5%. Complete clearance was reported in 23% (3/13) and 67% (8/12) at 60 days after commencing treatment with potassium hydroxide twice daily in each group respectively [31].

### Drawbacks

Four patients (two in each group) dropped out of the Rajouria *et al.* study due to noncompliance, and a table of side effects for the remainder of the participants showed erythema (14/23), edema (5/23), and burning (4/23) reported in those treated with 5% potassium hydroxide, though erosions (6/23) and ulceration (1/23) were also reported. Side effects from potassium hydroxide were common in the study by Uçmak *et al.*, with at least one side effect reported in 86.4% and 91.7% of those treated with 2.5% and 5% potassium hydroxide respectively. The exact number and nature of side effects were not reported. Tretinoin 0.05% cream appeared to produce milder adverse effects.

### Comment

The studies by Bazza and Ryatt and by Short *et al.* showed no significant benefit of potassium hydroxide in clearing molluscum. The Rajouria *et al.* study focused on a reduction in lesion count rather than clearance at 4 weeks. Although there was a significant reduction in mean lesion count with both treatments, there was no significant difference between the treatments and no placebo arm to assess the mean reduction in those without any treatment. Therefore, the study suggests potassium hydroxide (and tretinoin cream) improve the resolution of mollusca, but how much better than spontaneous resolution is unclear. This study was also nonblinded and nonrandomized, which is at high risk of selection and information bias, and it is unclear whether an intention-to-treat analysis was performed. Although the Uçmak *et al.* study was reported as randomized, allocation concealment was unclear. Despite efforts to blind study participants, it is unclear whether assessors had been blinded, and in fact the same observer was used for all follow-up visits, risking significant information bias. This study would also have benefitted from a control arm.

## Calcarea carbonica

### Efficacy

This homeopathic drug given daily for 15 days resulted in improvement in 93% (13/14) participants in the treatment arm and 17% (1/6) in the placebo arm of the trial (RR, 5.57; 95% CI, 0.93–33.54; not statistically significant) [43].

**Table 39.1** Summary of RCTs identified on molluscum contagiosum in otherwise healthy individuals.

First author, ref.	Intervention	Comparators	Study population	Sample size (n)	Study design	Duration of active treatment	Outcome measures	Main results	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Ormerod (1999) [32]	Sodium nitrite 5%–salicylic acid 5% cream	Salicylic acid 5% cream alone	Children (median age 6 years)	32	Double-blind RCT	3 months	Complete clearance rate after 3 months	Sodium nitrite 5%–salicylic acid 5% cream 75% (12/15) vs salicylic acid 5% cream 25% (4/15); completely cleared ( $P = 0.01$ )	Adequate Adequate Inadequate
Leslie (2005) [33]	Salicylic acid 12%, lactic acid 4% gel (Salatac)	(a) 10% phenol in 70% alcohol, (b) 70% alcohol (placebo)	Children (1–15 years)	114	Nonblinded RCT	6 months	Complete clearance rate after 6 months	Salatac 57% (21/37) vs phenol 42% (17/41) vs placebo 44% (16/36); completely cleared ( $P = 0.38$ )	Adequate Not applicable Adequate
Theos (2004) [35]	Imiquimod 5% cream	Vehicle	Children ( $4.7 \pm 1.9$ years)	23	Double-blind RCT	12 weeks	Complete clearance rate at week 12	Imiquimod 33.3% (4/12) vs vehicle 9.1% (1/12); completely cleared ( $P = 0.32$ )	Inadequate Inadequate Adequate
Burke (2004) [37]	Essential oil of Australian lemon myrtle	Vehicle	Children ( $4.6 \pm 3.1$ years)	31	Double-blind RCT	3 weeks	Proportion of patients with reduction of lesions >90%	Essential oil of Australian lemon myrtle 56% (9/16) vs vehicle 0% (0/15); met efficacy outcome ( $P < 0.05$ )	Adequate Adequate Adequate
Saryzadi (2004) [42]	Benzoyl peroxide 10% cream	Tretinoin 0.05% cream	Children (not reported)	30	Investigator-masked RCT	4 weeks	Complete clearance rate at week 6	Benzoyl peroxide 73% (11/15) vs tretinoin 0.05% 33% (5/15); completely cleared ( $P = 0.05$ )	Inadequate Inadequate Inadequate
Antony (2001) [44]	Cimetidine 35 mg/kg/day	Placebo	Children (1–16 years)	38	Double-blind RCT	3 months	Complete clearance rate after 4 months	Cimetidine 50% (4/8) vs placebo 46% (5/11); completely cleared ( $P > 0.05$ )	Inadequate Adequate Inadequate
Markum (2012) [40]	<i>Melaleuca alternifolia</i> + iodine	<i>Melaleuca alternifolia</i> alone Iodine alone	Children ( $6.3 \pm 5.1$ years)	53	3-arm RCT	30 days	Proportion of patients with reduction of lesions >90%	<i>Melaleuca alternifolia</i> +iodine 84% (16/19) vs <i>Melaleuca alternifolia</i> alone 17% (3/18) vs iodine alone 6% (1/16) met efficacy outcome ( $P < 0.01$ )	Inadequate Inadequate Adequate
Al Mutairi (2010) [26]	5% imiquimod cream	Cryotherapy	Children (2–8 years)	74	Nonblinded RCT	16 weeks	Complete clearance rate after 16 weeks	Imiquimod 92% (34/37) vs cryotherapy 100% (37/37) completely cleared ( $P = 0.3$ )	Inadequate Inadequate Adequate
Ohkuma (1990) [41]	10% povidone iodine solution and 50% salicylic acid plaster	10% povidone iodine solution alone, 50% salicylic acid plaster alone	Children (2–9 years)	35	3-arm RCT	Unclear	Complete clearance Time to cure	10% povidone iodine solution and 50% salicylic acid plaster 20/20 completely cleared at 26 days vs 10% povidone iodine solution alone 3/5 at 68 days vs salicylic acid plaster alone 7/10 at 47 days ( $P > 0.05$ )	Inadequate Inadequate Unclear

Continued

Table 39.1 Continued

First author, ref.	Intervention	Comparators	Study population	Sample size (n)	Study design	Duration of active treatment	Outcome measures	Main results	Study quality: Randomization <sup>a</sup> Blinding <sup>b</sup> Statistical analysis <sup>c</sup>
Coloe Dosal (2012) [27]	Cantharidin	Vehicle	Children (5–10 years)	29	Double-blind RCT	8 weeks	Complete clearance after 8 weeks	Cantharidin 15% (2/13) vs vehicle 6% (1/16) completely cleared ( $P > 0.05$ )	Adequate Inadequate Inadequate
Papadopoulos (2006) [25]	Imiquimod cream 5%	Vehicle	Children (2–12 years)	323 379	RCT	16 weeks	Complete clearance after 18 weeks	Imiquimod 24% (52/217) and (60/253) vs vehicle 26% (28/106) and 28% (35/126) completely cleared ( $P > 0.05$ )	Unclear Unclear Unclear
Bazza (2007) [28]	5% potassium hydroxide	0.9% normal saline	Children (2–12 years)	30	Double-blind RCT	3 weeks	Complete clearance after 12 weeks	5% potassium hydroxide 85% (17/20) vs 0.9% normal saline 85% (17/20) completely cleared	Unclear Adequate Inadequate
Short (2006) [29]	10% potassium hydroxide	Saline	Children (2–12 years)	20	Double-blind RCT	Unclear	Complete clearance up to 90 days	10% potassium hydroxide 70% (7/10) vs saline 20% (2/10) completely cleared (pooled with data above $P > 0.05$ )	Unclear Adequate Unclear
Rajouria (2011) [30]	5% potassium hydroxide	0.05% tretinoin cream	Children (6 months–14 years)	46	Nonrandomized controlled trial	4 weeks	Mean reduction in lesion count after 4 weeks	5% potassium hydroxide: $9.48 \pm 3.00$ SD to $1.67 \pm 0.58$ SD vs 0.05% tretinoin: $8.35 \pm 2.82$ SD to $2.00 \pm 1.00$ SD	Inadequate Inadequate Inadequate
Uçmak (2013) [31]	5% potassium hydroxide	2.5% potassium hydroxide	Children (15 months–18 years)	25	Patient-blinded RCT	60 days	Complete clearance after 60 days	5% potassium hydroxide 67% (8/12) vs 2.5% potassium hydroxide 23% (3/13) completely cured ( $P < 0.047$ )	Inadequate Inadequate Inadequate
Manchanda (1997) [43]	Calcareo carbonica	Placebo	Children and adults (0–30 years)	20	RCT	15 days	Improvement (not clear after what period)	Calcareo carbonica 93% (13/14) vs placebo 17% (1/6) improvement ( $P > 0.05$ )	Inadequate Adequate Inadequate

RCT, randomized controlled trial.

<sup>a</sup>Adequate, if clear description of method of randomization and concealment of allocation of randomization given.<sup>b</sup>Adequate, if assessors and participants were completely blinded to the study interventions.<sup>c</sup>Adequate, if an intention-to-treat analysis was carried out; that is, all patients originally randomized were included in the final main analysis.



**Drawbacks**

The study duration, time to resolution, dosing regimen, and adverse events were not reported and the study was not analyzed by an intention-to-treat principle. The number of dropouts (20/104 for the whole trial, including other skin conditions) is unclear for the molluscum participants.

**Comment**

For the above reasons, calcarea carbonica is not recommended as a treatment for molluscum.

**Cimetidine****Efficacy**

Oral cimetidine 35 mg/kg per day for 3 months added no notable benefit compared with placebo treatment: cimetidine 50% (4/8) versus placebo 46% (5/11), completely cleared after 4 months ( $P > 0.05$ ) [44].

**Drawbacks**

Half of the patients (19 of 38) dropped out. The reasons for withdrawal are not reported [44].

**Comment**

Cimetidine is not recommended in the treatment of molluscum contagiosum.

**Destructive methods such as cryotherapy, electrodesiccation, physical squeezing**

Apart from the Al Mutairi *et al.* study of the trial that compared imiquimod with cryotherapy [26], we were not able to identify any trials demonstrating the efficacy of these commonly used physical destructive treatments against each other or against no treatment. Although this study demonstrated high cure rates within a short period (37/37 completely cleared at 3 weeks), like most destructive methods this benefit must be balanced against tolerability in young children and adverse effects such as scarring.

**Implications for clinical practice**

Molluscum contagiosum is a self-limiting disease in the immunocompetent host. Treatment is not necessary in most cases, since natural resolution occurs. Topical treatments that do not leave scars and are not associated with severe adverse events may be tried in order to limit the spread, shorten the course of the disease, for cosmetic reasons, and/or to suppress accompanying symptoms. The decision to treat must take in to account these issues as well as patient factors, such as a child's age, history of atopy, secondary infection, and so on. It is unclear whether treatment of molluscum-associated dermatitis can limit spread of lesions [2].

Treatment options for mollusca that can be recommended on the basis of the existing scant evidence are 5% sodium nitrite with 5% salicylic acid cream for nonfacial lesions and cryotherapy. Salicylic acid preparations, phenol, cantharidin, imiquimod 5% cream, povidine iodine solution with salicylic acid plaster, oral calcarea carbonica, and cimetidine are not recommended on the basis of the data available. Most studies have small sample sizes and may, therefore, be underpowered to detect differences in clinical outcomes. A summary of trials for the treatment of molluscum contagiosum is presented in Table 39.1.

The evidence base for treatment and prevention of spread of mollusca is very poor considering it is such a common condition.

Future studies need to be much larger, randomized, include blinded assessment of responses, and should be prospectively registered and fully reported. The unit of analysis should be number of people and not numbers of lesions, and placebo or no treatment arms should be included. The importance of publishing studies with negative results should also be emphasized in order to avoid persistent use of treatments that have been proven not to work any better than placebo.

**Key points**

- Molluscum contagiosum in otherwise healthy people is self-limiting.
- Treatment is not necessary in most people.
- Many popular treatments, including physical destruction, have not been evaluated properly with well-designed, prospective, double-blinded randomized control trials.
- Topical sodium nitrite, cryotherapy, and possibly benzoyl peroxide preparations appear to shorten the duration of the disease.
- Current evidence suggests that salicylic acid preparations, phenol, cantharidin, imiquimod, and oral cimetidine are no more effective than placebo.

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# Impetigo

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## Background

### Definition

Impetigo (Figure 40.1) is a contagious superficial skin infection, characterized by superficial erosions covered with honey-colored crusts, most often on the face. A distinction is made between bullous and nonbullous impetigo. Impetigo may be primary or secondary to other skin diseases, such as atopic eczema.

### Incidence

Impetigo is most frequent in children; the incidence rates peak at 1–8 years of age. Population-based incidence rates are unknown. Impetigo is common in general practice, with incidence rates of around 20 episodes per 1000 children per year seen by general practitioners in the UK and the Netherlands [1–3].

### Etiology

In moderate climates, the primary pathogen in nonbullous impetigo is *Staphylococcus aureus*. However, in warm and humid climates, *Streptococcus pyogenes* or a combination of *S. pyogenes* and *S. aureus* are often isolated. The relative frequency of *S. aureus* infections has also changed with time. It was predominant in the 1940s and 1950s, and then group-A streptococci became more prevalent. In the last decade of the 20th century, *S. aureus* has been reported to have become more common again [4]. Bullous impetigo is a staphylococcal disease.

### Prognosis

Impetigo is believed to be self-limiting, taking several weeks to cure without intervention. However, no research is available to substantiate this statement. Prompt resolution usually occurs with adequate treatment. The course of the disease is usually mild, but sometimes general symptoms such as fever and lymphadenopathy occur. Streptococcal impetigo can be complicated by nephritis.

### Aims of treatment

Impetigo is treated to accelerate cure and to prevent spreading of the infection.

## Relevant outcomes

Clinical cure (clearance of crusts, blisters, and redness) is the most relevant outcome. Criteria such as relief of pain, itching, and soreness, and bacteriological cure can be considered as secondary outcomes.

## Methods of search

We found four systematic reviews [5–8], the Cochrane review published in 2012 [8] being an extended update of earlier versions [5,7]. As the Cochrane review, with 68 included randomized controlled trials (RCTs), is the most recent and most comprehensive one, it has provided the basis for discussing treatments in this chapter.

The Cochrane review included randomized trials of all interventions for impetigo by using the following search terms in Medline: impetigo (Medical Subject Headings, MeSH) or (MeSH) or impetigo (in title or abstract) or pyoderma (in title or abstract), in combination with the standard search strategy for identifying randomized trials. For this Cochrane review update, the literature was searched up to July 2010. Owing to space limitations, we only report here on nonbullous impetigo, and on the most relevant comparisons and outcomes.

## Questions

### What are the effects of treatments on the clearance of impetiginous lesions after 1 week?

#### Disinfecting treatments

##### Efficacy

**Versus placebo** We found one small randomized trial comparing hexachlorophene with placebo [9]. Scrubbing with hexachlorophene added no notable benefit to placebo treatment.

**Versus topical antibiotic treatment** One multicenter RCT compared hydrogen peroxide cream with fusidic acid cream/gel [10]. There was no significant difference in treatment effect, but there was a tendency towards a better effect of fusidic acid cream/gel. There was



**Figure 40.1** A child with impetigo (reproduced with permission of A.P. Oranje).

no significant difference between hexachlorophene and bacitracin ointment in a small and older study [9].

**Versus oral antibiotic treatment** There was no significant difference between hexachlorophene scrubbing and oral treatment with penicillin [9].

#### **Drawbacks**

Eleven percent of the patients using hydrogen peroxide cream reported mild side effects (not specified). No patient was withdrawn from the study because of side effects [10]. No adverse effects of scrubbing with hexachlorophene were recorded [9].

#### **Comment**

Disinfectants, such as povidone iodine and chlorhexidine advised in some guidelines, have not been compared with a placebo. Hydrogen peroxide cream showed good treatment results in a relatively large trial. However, the procedure for blinding in this trial was considered inappropriate.

#### **Implications for topical disinfectants in clinical practice**

There is no good evidence for the value of disinfecting measures in the treatment of impetigo.

### **Topical antibiotics**

#### **Efficacy**

**Versus placebo** Six studies compared a topical antibiotic with placebo treatment. Mupirocin has been studied in three placebo-controlled trials, all of which found a better effect with mupirocin [11–13]. One other RCT showed that fusidic acid was much more effective than placebo (55% of patients cured vs 13%) [14]. A result of similar magnitude was found for retapamulin versus placebo (86% vs 52%) [15].

**Versus each other** Several topical antibiotics have been compared directly. Mupirocin and fusidic acid were compared in four studies [16–19], none of which showed a significant difference in treatment effect. In a large study (>500 patients), the difference between retapamulin and fusidic acid was not statistically significant [20]. An old study found better results for gentamycin than for neomycin [21].

All other studies comparing topical antibiotics were small and each studied a unique comparison of two antibiotics.

**Versus oral antibiotics** When 10 RCTs that compared topical mupirocin with oral erythromycin were pooled [4,22–30], mupirocin was found to be significantly better than erythromycin [7]. In a small RCT, cephalexin and mupirocin were both significantly more effective than bacitracin cream [31]. A trial in patients with secondarily infected dermatitis found no difference between oral cephalexin and topical retapamulin ointment [32].

#### **Drawbacks**

RCT reports usually note few, if any, side effects with local antibiotics. The two studies comparing mupirocin with placebo reported none [11,12]. In studies comparing mupirocin with fusidic acid, the greasy nature of mupirocin was reported as a side effect in 7% of patients versus 1% [16]; minor itching/burning occurred in 5% versus 4%, respectively [18]. No side effects were reported in Gilbert's study [17]. Studies comparing erythromycin with mupirocin recorded gastrointestinal side effects in 23% versus 8% [4], none in either group [29], and an equal distribution between the two groups [23]. Hydrocortisone/potassium hydroxyquinoline caused two cases (3%) of mild staining [33]. In general, resistance rates against topical antibiotics such as fusidic acid and mupirocin will rise when the antibiotic is used excessively. Retapamulin caused itching in 7% of cases in one study [15] but only 1% in another study [20].

#### **Comments**

Most studies date back 20 years or more. Many RCTs deal with a range of (skin) infections, including impetigo. Only trials that reported separate results for the group of impetigo patients were included here. The follow-up periods and definitions of "cure" and "improvement" differ and are often not clear, making comparison difficult. There is a lack of placebo-controlled studies.

#### **Implications for topical antibiotics in clinical practice**

Although they are traditionally considered less effective than oral therapy, there is good evidence that local treatments are equal to or more effective than oral treatment. In general, oral antibiotics have more side effects, especially gastrointestinal side effects. Fusidic acid, mupirocin, and retapamulin are equally effective. Resistance patterns have changed since then. Contemporary and local characteristics and resistance patterns of the causative bacteria should always be taken into account when choosing treatment. When a large area is affected, or when the patient has general symptoms such as fever, oral therapy seems more appropriate. However, this assumption has never been tested properly.

### **Systemic antibiotics**

#### **Efficacy**

**Versus placebo** Only one small and inconclusive trial was found, comparing systemic antibiotics with placebo [9].

**Versus topical antibiotics** Discussed under topical antibiotics above.

**Versus each other** Two RCTs compared penicillin and erythromycin, both finding erythromycin to be more effective [34,35]. Cloxacillin was significantly superior to penicillin in two studies [36,37]. All other comparisons were each made in only one study,



and none of these showed a relevant difference between treatments.

### Drawbacks

The incidences of side effects were:

- azithromycin – 17%, mainly mild gastrointestinal [38];
- cephalexin – 11%, mainly mild gastrointestinal [38], 11% mainly diarrhea [39], no adverse effects in one study [34];
- cefdinir – 16%, mainly diarrhea [39];
- erythromycin – up to 17% gastrointestinal side effects, mainly diarrhea [40].

### Comments

Many RCTs have been carried out on a range of “soft-tissue” infections, with a subset of impetigo patients. Only trials reporting separate results for the group of impetigo patients were considered in this chapter, although it should be pointed out that most trials in patients with “soft-tissue” infections did not provide results for impetigo separately.

There is a lack of placebo-controlled studies. Resistance rates of the bacteria were determined in some studies, and differed from study to study. The follow-up periods differ widely between the studies, making comparison difficult.

### Implications for use of systemic antibiotics in clinical practice

There is good evidence that local treatment is equal to or more effective than oral treatment. Macrolide antibiotics provide better treatment results than penicillin. In general, oral antibiotics have more side effects than topical treatments, especially gastrointestinal side effects. Most studies date back 20 years or more, and resistance patterns have changed since then. Contemporary local characteristics and the resistance patterns of the causative bacteria should always be taken into account when choosing treatment.

When a large area is affected, or when the patient has general symptoms such as fever, oral therapy seems preferable. As mentioned above, this assumption has never been tested properly.

### Key points

- The natural history of impetigo is not known.
- Few placebo-controlled studies have been done.
- Many different antibiotic treatments have been studied against each other, often in small studies showing no significant differences.
- There is no evidence supporting the value of disinfecting treatments.
- Topical antibiotics such as mupirocin and fusidic acid are equal to or more effective than oral antibiotics such as erythromycin and have fewer side effects.
- Macrolide and cephalosporin antibiotics are more effective than penicillins that are not resistant to beta-lactamase.
- For extensive infections accompanied by general symptoms such as fever, oral antibiotics may be preferable.
- Resistance patterns in causative bacteria change over time, and this should be taken into account when choosing a therapy for impetigo.

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# Athlete's foot

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## Background

### Definition

Athlete's foot, or *tinea pedis*, is commonly caused by dermatophyte invasion of the skin of the feet. It is clinically presented as interdigital, moccasin, or vesicobullous forms, with interdigital being the most common. Moccasin infection affects soles, heels, and sides of the feet, characterized by dry and hyperkeratotic skin. With less frequency, vesicobullous is the most severe form of athlete's foot. It appears as an acute and intense inflammation with vesicles, pustules, and bubbles, usually on the soles of feet [1–3] (Figure 41.1).

### Incidence/prevalence

It has been estimated that 15% of the general population have athlete's foot. It is thought to occur when individuals regularly use communal changing rooms and swimming pools. There are studies indicating higher prevalence in male and elderly people [4,5].

### Etiology

Athlete's foot is usually caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes* var. *interdigitale*, and *Epidermophyton floccosum*. Individuals with athlete's foot may be susceptible to secondary bacterial infection with, for instance, group A streptococcus [6].

### Diagnostic tests

Diagnosis of dermatophytosis is based on clinical and laboratory data. Clinical diagnostic procedure must include physical exam of the lesions and epidemiological history survey, whereas mycological tests consist of microorganisms visualization in microscopy and culture growth [2,7,8].

### Aims of treatment

The management of dermatophytosis consists of topical formulations, oral therapy, or a combination of them. An oral drug is needed when the affected area is wide, the patient is immunocompromised, or the disease is chronic or recurrent with failure on topical treatment [2,9].

The aim of treatment is to decrease signs and symptoms, such as redness, itching, and flaking, and also to eradicate the infection,

being that the course of treatment is partially determined by the severity level [1].

Topical antifungals are available as over-the-counter drugs in most countries and are divided into two main classes: azoles, in which the mechanism of action is fungistatic, and allylamines, acting as fungicides. Other “non-azoles” and “non-allylamines,” such as tolnaftate and undecenoic acid, are also commercialized over the counter and, commonly, cost less than the others [2,10].

### Relevant outcomes

The efficacy outcomes evaluated were mycological cure at the end of treatment (MCET) and sustained cure (SC), defined as cure obtained up to 7 days after therapy conclusion and cure maintained for at least 14 days following the end of treatment, respectively. Efficacy of treatment was evaluated by meta-analysis, and the mycological cure was the main outcome considered, evidenced by microscopic negative or absence of growth of dermatophytes in culture [11].

### Methods of search

Systematic reviews and randomized clinical trials (RCTs) were identified using a search strategy published elsewhere [11]. This was updated to June 2012 using the same strategy. We included studies that compared the use of antifungals among themselves or with placebo in the treatment of any clinical form of athlete's foot. Only studies that had patients diagnosed mycologically with the disease were included.

## Questions

### How effective are allylamine creams in the treatment of athlete's foot?

Two meta-analysis published comparing allylamines (terbinafine and naftifine 1%) with placebo, used for 1–4 weeks, show that the two antifungals are similarly effective and better than placebo [5,10].

In a third meta-analysis were identified 12 RCTs ( $n = 1418$ ) comparing naftifine 1% and terbinafine 1% or 3% with placebo,



Figure 41.1 Athlete's foot.

used for 1 day (single-dose) to 28 days. For both efficacy outcomes, allylamines were better than placebo. In terms of MCET, meta-analysis of data from nine RCTs estimated the pooled odds ratio (OR) as 5.87 (95% confidence interval [CI], 2.46–14.01) and number needed to treat (NNT) of 3. For SC outcome, combined data from 11 studies, with follow-up period lasting from 2 to 12 weeks after the cessation of treatment, resulted in an OR of 14.22 (95% CI, 9.49–21.32) and NNT of 2 [12].

### How effective are azole creams in the treatment of athlete's foot?

Two systematic reviews were found comparing the azoles clotrimazole 1%, tioconazole 1%, bifonazole 1%, econazole 1%, and miconazole 2% with placebo, used for 4–6 weeks. The antifungals were similarly effective and better than placebo [5,10].

Another systematic review ( $n = 1223$ ) compared econazole 1%, miconazole 2%, oxiconazole 1%, sertaconazole 2%, and clotrimazole 1% with placebo, used for 28–42 days [12]. For MCET, the data interpolation from seven RCTs resulted in an OR of 5.54 (95% CI, 3.01–10.19) and NNT of 3. For SC outcome, pooled data of four trials with follow-up period lasted from 2 to 4 weeks after the cessation of treatment shows an OR of 6.64 (95% CI, 4.65–9.48) and NNT of 2 [12].

### How do allylamine creams compare with azole creams in curing athlete's foot?

A meta-analysis of nine RCTs ( $n = 1003$ ) indicate better mycological cure rate with allylamines cream (terbinafine and naftifine 1%) in comparison with azoles cream (clotrimazole 1–2% and bifonazole 1%), used for 4–6 weeks. The relative reduction in treatment failure was 37%, favoring allylamines (relative risk [RR], 0.63; 95% CI, 0.42–0.94) [5].

Considering different treatment regimens, data collected at 6 weeks from five trials ( $n = 962$ ), which compared terbinafine 1%

used for 1 week with clotrimazole or miconazole 1% used for 4 weeks, did not show a statistically significant difference in treatment failure (RR, 0.75; 95% CI, 0.33–1.72). However, there was considerable variation in the results of the individual trials [5].

In the study of Patel *et al.* [13], terbinafine was more effective than clotrimazole after 1 week of therapy (RR, 1.51; 95% CI, 1.16–1.98), but there were no differences between the classes in the following weeks.

We performed a meta-analysis of two studies ( $n = 955$ ) [14,15], which compared terbinafine 1% cream twice daily for 1 week and clotrimazole 1% cream twice daily for 4 weeks. Terbinafine was better than clotrimazole for the MCET outcome (OR, 0.28; 95% CI, 0.09–0.85), without differences for the SC outcome, 6 weeks after the end of the treatment (OR, 0.40; 95% CI, 0.07–2.38). A result favoring the use of allylamines (RR, 0.88; 95% CI, 0.78–0.99) was also obtained by Hart *et al.* [10], although some language bias was detected.

In another systematic review, eight trials ( $n = 1300$ ) comparing oxiconazole 1%, clotrimazole 1%, miconazole 2%, or bifonazole 1% with naftifine and terbinafine, both 1%, were pooled. The OR of 0.55 obtained for MCET was statistically favorable to allylamines (95% CI, 0.33–0.92) with an NNT of 41. The results of nine RCTs ( $n = 1523$ ) were interpolated for the SC outcome, giving an OR of 0.39 (95% CI, 0.22–0.67) and NNT of 13, in favor of the allylamines [12].

### How effectively do creams that can be bought in the supermarket cure athlete's foot?

Meta-analysis data indicates that tolnaftate (RR, 1.56; 95% CI, 1.05–2.31) and undecenoic acid (RR, 2.83; 95% CI, 1.91–4.19) are more effective than placebo [5]. We performed a meta-analysis of RCTs comparing ciclopiroxolamine (0.77% and 1%) used for 4 weeks with placebo (three trials,  $n = 654$ ) [16–18]. The ORs obtained were statistically favorable to the antifungal: 6.67 (95% CI, 3.47–12.80) for MCET and 8.98 (95% CI, 2.27–35.53) for the SC outcome. Other studies have similar results [5,10].

Finally, we performed a meta-analysis of four trials ( $n = 711$ ) [19–22] comparing butenafine 1% cream with placebo, used for 1–4 weeks. A result favoring the use of butenafine was obtained for MCET (OR, 7.25; 95% CI, 2.25–23.38) and SC (OR, 12.33; 95% CI, 6.16–24.71) outcomes.

### Are oral drugs more effective than topical formulations in the treatment of athlete's foot?

The major advantage of oral drugs is a decrease on the duration of the treatment, which can improve a patient's compliance [4]. On the other hand, its cost is higher than the treatments based on topical agents, including the costs with medical care.

One RCT ( $n = 137$ ) compared the efficacy of interdigital tinea pedis treatment with oral (terbinafine 250 mg once daily for 1 week) and topical antifungal (clotrimazole 1% cream twice daily for 4 weeks). At week 4, the mycological cure rates were similar for the two drugs (72% for allylamine and 71% for clotrimazole). Although at week 1 the patients treated with terbinafine showed more rapid clinical improvement, higher levels of relapse were observed between weeks 4 and 12 after treatment with this drug (17% vs 5%). Both treatments were well tolerated, with incidence of adverse events equal between the groups [23].

Considering the absence of more studies, it is cautious to reserve treatment with oral antifungals only for several or relapsing cases of athlete's foot, when there is no topical treatment response [24].



## What are the most effective oral drugs in the treatment of athlete's foot?

The efficacy of oral drugs is not influenced by the type of tinea pedis [4].

A meta-analysis of 12 RCTs ( $n = 700$ ) showed no significant differences between terbinafine (250 mg/day for 2 weeks) and itraconazole (100 mg/day for 4 weeks); between fluconazole 50 mg and either itraconazole 100 mg or ketoconazole 200 mg, used for 6 weeks; or between griseofulvin 1000 mg and ketoconazole 200 mg, used for 4 weeks [4].

For the same treatment length (2 weeks), terbinafine 250 mg was more effective than itraconazole 100 mg. Moreover, terbinafine 250 mg cures 52% more patients than griseofulvin 500 mg, when used once daily for 4–6 weeks [4].

Adverse effects were reported for all drugs, with gastrointestinal effects, such as diarrhea and nausea, being the most commonly reported. There were no long-duration or harming adverse events [4]. The oral therapy with terbinafine, itraconazole, and fluconazole was associated with low incidence of adverse events in an immunocompetent population [25].

## What are the most effective topical drugs in the treatment of athlete's foot?

We applied a random-effects Bayesian mixed treatment comparisons (MTC) model to combine placebo-controlled and direct topical antifungals comparison trials. Our analysis included 41 clinical trials published until June 2012 retrieved through a systematic review of the same databases used for conventional meta-analysis [11].

Our analysis did not show statistically significant differences among all pairwise antifungals assessed (bifonazole, butenafine, clotrimazole, ciclopiroxolamine, econazole, flutrimazole, ketoconazole, miconazole, naftifine, oxiconazole, sertaconazole, and terbinafine) for the MCET outcome.

For the SC outcome, the ORs for butenafine, naftifine, and terbinafine were statistically superior to oxiconazole: 5.10 (95% CI, 1.16–22.47), 4.61 (95% CI, 1.23–17.33), and 6.05 (95% CI, 1.74–21.05), respectively. Terbinafine also showed better response when compared with clotrimazole (OR, 2.88; 95% CI, 1.27–6.53). Terbinafine, butenafine, and naftifine, which occupied the first three places in the ranking, might be the best strategies for cure maintenance.

## Drawbacks

Our analysis of published clinical trials has showed no differences in safety in all direct comparisons made between antifungals and placebo and among antifungal class. Few serious adverse events were reported, and the most common adverse events reported were burning, stinging, and itching, all confined to the site of application [11,12].

All oral antifungals were associated with the occurrence of adverse events. The lowest prevalence of events was obtained with fluconazole (11%) and the highest with terbinafine (18%) [4].

## Comments

There is consistent evidence regarding the superiority of antifungals in comparison with placebo. For athlete's foot, allylamines are better than azoles in providing and maintaining mycological cure.

Oral antifungals are not more effective than topical ones in the management of athlete's foot. Additionally, higher rates of infection relapse, adverse events, and costs of the treatment were observed in patients treated with oral agents [7].

## Implications for clinical practice

All topical antifungals (azoles, allylamines, butenafine, ciclopiroxolamine, tolnaftate, and undecenoic acid) can be recommended to the treatment of athlete's foot.

Allylamines are superior to azoles in obtaining and maintaining cure, with the advantage of requiring a shorter period of time that can be associated with greater rates of compliance. Nevertheless, owing to their higher cost compared with other antifungals, an individual analysis for each patient must be done.

Oral therapy must be considered only for severe infections or in relapses cases.

## Key points

- All topical antifungals are better than placebo in the treatment of athlete's foot.
- Direct comparisons of allylamines versus azoles used in the treatment of athlete's foot show allylamines to be generally more efficacious than azoles.
- MTC results do not show statistical differences among the antifungals considering the MCET outcome. Terbinafine, butenafine, and naftifine might be the best strategies for cure maintenance.
- There is evidence to suggest that oral drugs are no more effective than creams in producing a cure for athlete's foot and still produce more adverse events.
- No differences were found in safety in all direct comparisons established between antifungals and placebo and between antifungals with each other.

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# Pityriasis versicolor

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## Background

### Definition

Pityriasis versicolor (also known as tinea versicolor) is an infection of the skin caused by the lipophilic yeast genus *Malassezia*, which contains at least 14 species with the modern molecular-genetically based taxonomy; in most cases it is thought to be due to *Malassezia globosa*, although other species such as *Malassezia sympodialis* are likely involved in some cases [1]. The disease is manifested by very thin, scaly plaques that can be hyperpigmented, hypopigmented, or erythematous (Figure 42.1). Lesions are generally asymptomatic, but can be associated with pruritus. The rash may be accompanied by hyper- or hypopigmentation that often persists long after the organism is eradicated. The eruption most commonly affects the torso, neck, ears, and the pubis, but can be widespread. The face may be affected, especially in children [2].

### Incidence/prevalence

The incidence of pityriasis versicolor is not well studied. As the organism grows best in warm and wet conditions, it is more common and more extensive in tropical climates. The prevalence was 2.1% (22/1024) among a representative sample of young Italian sailors [3]. The prevalence was 1.8% among textile workers in Adana, Turkey, 15.5% (140/902) in a fishing village in Rio Seco, Venezuela, 16.6% among a random sample of adults in the Central African Republic, and 3.1% among 4267 people in Sao Paulo, Brazil [4–7]. In a total population survey in Karonga district, Malawi, 8% (4915/61 735) were found to have extensive pityriasis versicolor and an additional 9.9% (6085 people) had mild disease [8].

### Etiology

Pityriasis versicolor is caused by the lipophilic yeast genus *Malassezia*, mostly due to *M. globosa*.

### Prognosis

Untreated, the disease may lessen or remit in colder weather but almost invariably reappears in hot weather. Annual recurrences during hot weather are common in treated and untreated patients.

### Diagnosis

The diagnosis can be established by KOH staining of scales obtained from affected scaly plaques. On microscopy, the organism is easily recognized as spores and hyphae that resemble “spaghetti and meatballs” (Figure 42.2). Identification is enhanced by the addition of blue–black ink and a wetting agent to the KOH preparation. Under Wood’s light examination, pityriasis versicolor fluoresces a light yellow or golden color. The organism can also be cultured, but the culture technique is difficult and not readily available.

### Aims of treatment

The aim of treatment is the eradication of the organism, which can be verified by negative KOH preparations, and resolution of the rash. The hyper- or hypopigmentation may persist after the organism has been eradicated. The aim of interventions for prevention is to prevent annual recurrences during hot weather.

### Relevant outcomes

The primary outcomes of treatment are eradication of the organism, verified by KOH preparations, and resolution of the rash. The primary outcome of prevention is to stop recurrences in hot weather.

### Methods of search

We searched the Cochrane Library, LILACS, Medline, and Embase from inception until August 2012.

## Questions

### What are the effects of topical treatments used for the treatment of pityriasis versicolor?

#### Efficacy

We found one systematic review by Hu and Bigby which showed most topical treatments are effective when compared with placebo, but the data are less conclusive when comparing topical treatments with each other with different dosages and durations [9]. Randomized controlled trials of topical treatments for pityriasis

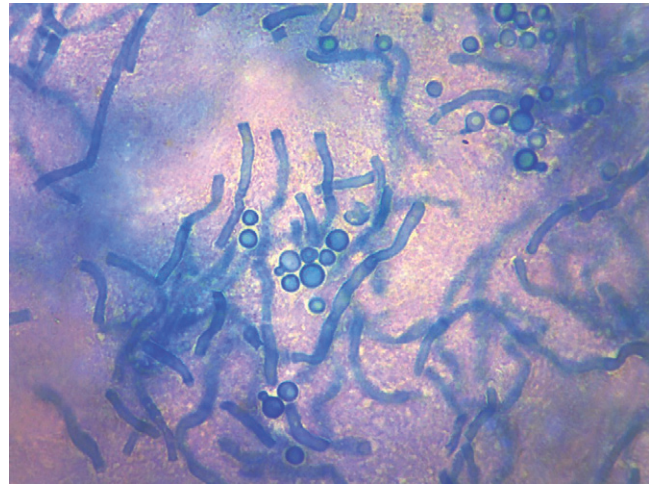


**Figure 42.1** Pityriasis versicolor most commonly affects the torso but can be widespread.

versicolor have increased over the past decade, but many still involve only a small number of patients [9]. Most topical treatments used to treat pityriasis versicolor (including imidazole antifungal creams or shampoos, zinc pyrithione shampoo, selenium sulfide shampoo, and sulfur–salicylic acid shampoo) are effective when compared with placebo with numbers to treat (NNTs) of 1–2. Topical terbinafine is less effective than other available topical treatments. The largest number of randomized studies on topical imidazoles has involved ketoconazole, followed by clotrimazole and bifonazole.

Of the non-imidazole topical agents, zinc pyrithione, sulfur–salicylic acid, and selenium sulfide have shown the greatest response differences in comparison with placebo. Some studies have assessed the use of other non-imidazole topical agents such as lactic acid, adapalene, 1% diclofenac gel, and *Artemisia sieberi* lotion [10–14]. One small study showed 10% lactic acid solution to have similar effects as clotrimazole 1% solution at the end of 4 weeks, but at the end of 2 weeks more patients in the lactic acid group showed resolution, with a risk difference (RD) of 56 (95% confidence interval [CI], 33–79) and an NNT of 2 [13]. Two studies compared *Artemisia sieberi* lotion with clotrimazole lotion, and after 4 weeks of treatment both studies showed *Artemisia sieberi* to have superior effects to clotrimazole with RDs of 21 (95% CI, 3–39) and 19 (95% CI, 4–33); the NNTs were 5 and 6, respectively [10,11]. In the one study comparing 1% diclofenac gel with clotrimazole cream and placebo cream, 1% diclofenac gel was inferior to treatment with clotrimazole (RD, –36; 95% CI, –58 to –14) but better than placebo (RD, 56; 95% CI, 37–75) [14]. One study compared adapalene with ketoconazole cream, and the results did not reach statistical significance (RD, 8; 95% CI, –12 to +27) [12].

Most trials comparing different active agents or different treatment regimens are underpowered to detect clinically meaningful differences [9]. However, the data suggest that longer durations of



**Figure 42.2** The diagnosis can be established by 10% KOH–50% Parker ink staining of scales obtained from affected scaly macules. On microscopy, the organism is easily recognized as spores and hyphae that resemble “spaghetti and meatballs.”

treatment and higher concentrations of active agents produce greater cure rates. In individual studies, the differences often do not reach statistical significance.

Although optimal regimens have not been established, the data suggest that 1–4 weeks of treatment can be recommended. Ketoconazole shampoo is applied to affected areas, left on for 5–10 min and then washed off. Treatment is repeated daily for 1–4 weeks. The imidazole creams are applied once or twice daily for 1–4 weeks. Creams are more costly than shampoos and no more effective, and therefore are less cost-effective. Selenium sulfide or zinc pyrithione shampoo is applied to affected areas for 5–10 min and then showered off. Treatment is repeated daily for 1–4 weeks. Many of the studies lack follow-up past 1 month after completing treatment, so it is difficult to assess the duration of cures.

### Drawbacks

Topical treatments for pityriasis versicolor are generally well tolerated. They may cause skin irritation or contact allergy. Selenium sulfide is more likely to cause skin dryness and irritation than other available treatments and has a strong odor.

### Comment

The topical treatment of pityriasis versicolor is an area in which evidence and experience coincide.

### Implications for clinical practice

Most topical treatments used to treat pityriasis versicolor (including imidazole antifungal creams or shampoos, zinc pyrithione shampoo, selenium sulfide shampoo, and sulfur–salicylic acid shampoo) are effective when compared with placebo with NNTs of 1–2. Data suggest that longer durations of treatment and higher concentrations of active agents produce greater cure rates. Terbinafine is less effective than other available topical treatments. Selenium sulfide is more likely to cause skin dryness and irritation than other available treatments.



## What are the effects of systemic treatments used for pityriasis versicolor?

### Efficacy

We found one systematic review [9]. Randomized controlled trials of systemic treatments for pityriasis versicolor are generally of low to moderate quality, usually involving small numbers of patients and many lacking blinding or intention to treat analysis [9]. Most systemic treatments used to treat pityriasis versicolor (including oral triazoles and imidazoles) are effective when compared with placebo with NNTs of 1–2. The data are lacking for the efficacy of oral terbinafine in pityriasis versicolor.

Trials comparing different active agents or different treatment regimens are underpowered to detect clinically meaningful differences [9]. However, the data suggest that longer durations of treatment and higher doses produce greater cure rates. In individual studies, the differences often do not reach statistical significance.

Although optimal regimens have not been established, the data suggest that ketoconazole 200 or 400 mg daily for 7–10 days, itraconazole 200 mg daily for 5–7 days, or fluconazole 300 mg weekly for 2–4 weeks can be recommended. One study has also shown pramiconazole 200 mg for 2–3 days to be better than placebo with an RD of 69 (95% CI, 49–89) and an NNT of 2 [15]. Response rates tended to be dose dependent, with single-dose regimens (e.g., ketoconazole 400 mg or fluconazole 450 mg or intraconazole 400 mg) being less effective. However, the NNTs are large and the confidence intervals wide in individual studies.

### Drawbacks

All of the imidazoles and triazoles inhibit the enzyme cytochrome P450 system. Therefore, these agents have many drug–drug interactions. Concomitant administration with other drugs which are metabolized by the cytochrome P450 system should be monitored closely. These agents should not be administered in patients on cisapride, astemizole, and terfenadine owing to potential rare cardiovascular adverse events such as arrhythmias, torsade de pointes, and death.

Ketoconazole carries a **Black Boxed Warning** issued by the US Food and Drug Administration (FDA) because it has been associated with hepatotoxicity, including some fatalities. The frequency is low (134 cases per 100 000 person-months (95% CI, 37–488) in one study), but it is the highest among the oral imidazole antifungals [16]. Liver function tests should be checked if the duration of treatment exceeds 1 week. Ketoconazole administration is contraindicated with use of cisapride for the reasons stated above. High doses of ketoconazole may suppress adrenocortical function. In clinical trials, nausea/vomiting (3–10%), pruritus (2%), and abdominal pain (1%) were reported. Diarrhea, dizziness, fever, gynecomastia (androgen receptor antagonist), and headache occur less frequently.

Itraconazole, a triazole, carries a **Black Boxed Warning** from the FDA for association with development of congestive heart failure (CHF), especially in patients with a history of CHF. Coadministration with cisapride, pimozide, midazolam, triazolam, simvastatin, lovastatin, quinidine, dofetilide, and levomethadyl is contraindicated due to itraconazole's inhibition of the cytochrome P450 system. Rare cases of serious cardiovascular adverse events (including death, QT prolongation, ventricular tachycardia, and torsade de pointes) have been observed when itraconazole is administered with those stated agents. Itraconazole has been associated with rare cases of serious hepatotoxicity (including fatal cases and cases within the first week of treatment). It is, therefore, not recom-

mended for use in patients with active liver disease, elevated liver enzymes, or prior hepatotoxic reactions to other drugs (www.uptodate.com).

In clinical trials with itraconazole, nausea (11%), edema (4%), hypertension (3%), headache (4%), fatigue (2–3%), malaise (1%), fever (3%), rash (9%), pruritus (3%), decreased libido (1%), hypertriglyceridemia, hypokalemia (2%), abdominal pain (2%), anorexia (1%), vomiting (5%), diarrhea (3%), abnormal liver function tests (3%), albuminuria (1%), and dizziness (2%) were reported (www.uptodate.com).

In clinical trials with fluconazole, headache (2–13%), rash (2%), nausea (4–7%), vomiting (2%), abdominal pain (2–6%), and diarrhea (2–3%) were reported. Hepatitis and liver function test elevations are rare and less common than with other azoles. Serious adverse reactions are rare (www.uptodate.com).

### Comment

Treatment with oral azoles is an area in which evidence and experience coincide.

### Implications for clinical practice

Extensive pityriasis versicolor can be successively and safely treated with the oral imidazole antifungals. Because of their effect on the cytochrome P450 system and the associated implications on concentrations of coadministered medications, close evaluation of a patient's medication list is recommended. Data suggest that ketoconazole 200 or 400 mg daily for 7–10 days, itraconazole 200 mg daily for 5–7 days, or fluconazole 300 mg weekly for 2–4 weeks can be recommended.

## What are the effects of topical and systemic regimens used to prevent recurrences of pityriasis versicolor?

### Efficacy

We found one systematic review [9]. There is limited evidence from clinical trials. Itraconazole 200 mg twice daily once per month for 6 months was effective in preventing recurrences compared to placebo (response difference 32%; 95% CI, 20–43%; NNT, 4; 95% CI, 3–5). We found no randomized controlled trials using ketoconazole or fluconazole to prevent recurrences. Case series suggest that ketoconazole weekly or fluconazole monthly may be effective.

We found one randomized controlled clinical trial of topical regimens to prevent recurrences [17]. Two different dosing schedules of topical bifonazole were studied. Conclusions could not be drawn from this study [17].

### Drawbacks

See above.

### Comment

Weekly or monthly doses of azole antifungals are commonly used to prevent recurrences of pityriasis versicolor. Randomized controlled data to support their use are scant for itraconazole and were not found for ketoconazole and fluconazole.

### Implications for clinical practice

A small randomized clinical trial suggests that itraconazole 200 mg twice daily once a month is effective in preventing recurrences. Optimal regimens for ketoconazole and fluconazole have not been established. Optimal regimens for topical prevention have not been established.

## Key points

- The diagnosis of pityriasis versicolor can be easily established by KOH staining of scrapings from affected skin.
- Most topical treatments used to treat pityriasis versicolor (including imidazole antifungal cream or shampoos, zinc pyrithione shampoo, selenium sulfide shampoo, and sulfur/salicylic acid shampoo) are effective when compared with placebo with NNTs of 1–2.
- Post-inflammatory hypopigmentation may persist for several months after successful treatment.
- Extensive pityriasis versicolor can be successively and safely treated with the oral azole antifungals.
- Data suggest that ketoconazole 200 or 400 mg daily for 7–10 days, itraconazole 200 mg daily for 5–7 days, or fluconazole 300 mg weekly for 2–4 weeks can be recommended.
- Optimal regimens for ketoconazole and fluconazole have not been established.
- Caution must be taken with administering oral imidazoles and triazoles with medications which are metabolized by the cytochrome P450 system. Concomitant administration with cisapride, terfenadine, or astemizole is contraindicated.
- Data on prevention of recurrences are sparse. One study has suggested that itraconazole 200 mg twice daily once per month for 6 months was effective in preventing recurrences compared with placebo.
- Optimal regimens for topical prevention have not been established.
- Randomized, controlled clinical trials are needed to establish optimal topical and oral regimens to prevent recurrences.

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# Onychomycosis

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## Background

### Definition

Onychomycosis is a fungal infection of the nail caused predominantly by anthropophilic dermatophytes, less commonly by yeast (*Candida* spp.), and by non-dermatophyte mold infections [1–3]. Onychomycosis may present with hyperkeratosis, subungual debris, thickening, or discoloration of the nail plate (Figure 43.1). Total nail dystrophy may also result with advanced onychomycosis [3].

### Incidence/prevalence

Onychomycosis is the most common nail disorder in adults. It accounts for approximately 50% of all nail diseases [4,5] and has increased in individuals over the last 80 years [3]. In North American centers, the prevalence of onychomycosis is between approximately 6.5 and 13.8% [4,6–8]. Onychomycosis predominantly affects toenails in comparison with fingernails; in some reports, the ratio of toenail:fingernail onychomycosis ranges from 4:1 to 19:1 [4,7,9,10].

### Etiology/risk factors

Predisposing factors for onychomycosis include tinea pedis, positive family history, increasing age, male gender, trauma, immunosuppression, diabetes mellitus, poor peripheral circulation, and smoking [3,4,6,7,11–18]. In addition, for fingernails, persistent exposure to water, the use of artificial nails, and trauma induced by pushing back the cuticles and aggressive manicuring may also be predisposing factors.

### Prognosis

Onychomycosis can be effectively treated with systemic and/or topical antifungal agents, as well as device-based therapies. Traditional systemic agents used to treat onychomycosis include griseofulvin. The newer oral agents used to treat onychomycosis are terbinafine, itraconazole, and fluconazole [19–26]. Recent available data suggest that the triazoles ravuconazole and posaconazole are effective for this indication [27,28]. Topical treatments include ciclopirox and amorolfine nail lacquers [29,30]. Only ciclopirox nail lacquer 8% has been approved in the USA for the treatment of onychomycosis [31].

Relapse of onychomycosis, especially in the toenails, is not uncommon, particularly in predisposed individuals. The reasons

why fingernail onychomycosis responds better than toenail disease may be related to the fact that perfusion of the upper extremity is generally better than that of the lower extremity; this may result in improved drug delivery to the fingers in comparison with the toes. Also, fingernails have a faster rate of outgrowth in comparison with toenails (3 mm/month compared with 1 mm/month) [32], resulting in the infected fingernail growing out faster than its lower extremity counterpart.

### Aims of treatment

Onychomycosis may be a cosmetic problem, especially when fingernails are infected [33]. The treatment objectives are to reduce the fungal burden within the nail, ultimately curing the fungal infection, and to promote healthy regrowth of affected nails. In some instances, when onychomycosis is associated with a degree of morbidity – for example, pain, discomfort, or soft-tissue infection – timely treatment may help eliminate symptoms and prevent complications that could be associated with more severe consequences [34].

### Relevant outcomes

The most commonly reported therapeutic measure of efficacy is mycological cure, which is defined by most as a negative light-microscopic examination and negative culture. There are several methods by which clinical improvement has been assessed. Some studies have used the parameter of clinical success, which is defined as “cleared” or “markedly improved” (90–100% clear nail) [35]. Others have defined clinical success as cure or improvement sufficient to reduce the involved area of the target nail to less than 25% at the end of therapy [36]. Another term that has been used is “clinical effectiveness,” which is taken to be mycological cure and at least 5 mm of new clear toenail growth [37]. Clinical cure refers to the post-therapy nail appearing completely cured to the naked eye. The complete cure rate is the combined result of mycological and clinical cure.

These outcomes are typically reported in clinical trials in which one toenail is chosen as the target, and “cure” is based on the target toenail alone. While such standards are necessary to provide points of comparison for clinical efficacy, all affected nails would be cured if a regimen was “successful.” There is a paucity of clinical data including outcomes for all affected toenails during oral therapy, and there is evidence to suggest that not all toenails can be expected



**Figure 43.1** Infection of the nail of the left great toe in a 47-year-old nondiabetic male who had no other health problems. He gave a history of a nail abnormality that had persisted for approximately 15 years, possibly related to previous nail trauma. The thickened nail had large areas of yellowish-white discoloration, typical of fungal nail infection. Culture revealed infection with the dermatophyte fungus *Trichophyton rubrum*.

to have equivalent degrees of clinical cure [38,39]. Clinicians should keep in mind that the outcomes measured in clinical studies may not adequately represent all patients being treated for onychomycosis.

The limitations of standard microscopy and culture methods have been recognized for years, particularly in relation to the high rate of false-negative cultures, but until recently no other reliable methods of fungus identification have been available. Reports on the use of molecular biological methods to identify fungal DNA are increasing [40–44]. These molecular methods provide faster identification relative to the standard microscopy/culture methods. It remains to be seen what impact such analysis may have on fungal treatment. Greater use of such analyses can be expected in the future, particularly if it can be conclusively demonstrated that such methods can provide an analysis of viable fungus present in nails with higher reliability than standard microscopy/culture methods.

## Methods

PubMed, the Cochrane Library, and Embase databases were searched in June 2012 for English-language publications for the best evidence for the different clinical questions presented in this chapter based on the hierarchy principle: first, systematic reviews; second, randomized clinical trials; and third, nonrandomized evidence. Evidence was graded using the quality-of-evidence scale system presented in Chapter 7, and the quality of randomized clinical trials was judged on a clear description of the randomization and concealment of allocation methods, blinding, the type of analysis (i.e., intention-to-treat or per protocol), and the sample sizes.

Onychomycosis caused by *Candida* spp. and nondermatophyte molds is less common and will not be considered in this chapter. The efficacy data presented for the different antifungals would be for the treatment of onychomycosis caused by dermatophytes.

The use of the nail lacquers ciclopirox and amorolfine are discussed, as these agents are approved for use in onychomycosis. There are many anecdotal reports of various other topical agents being effective for the management of onychomycosis; however,

published reports of the efficacy of topical agents in onychomycosis in the indexed, peer-reviewed literature are far fewer. Other clinical trials have included tioconazole 28% solution, bifonazole with urea, fungoid tincture, miconazole, and tea-tree oil. The authors would like to bring to your attention that, subsequent to the literature search for this review, clinical trials results have been published for a new topical solution for the treatment of onychomycosis, efinaconazole 10%. Consequently, the evidence for this new topical treatment is not presented.

The use of other topical agents and cosmetic procedures such as debridement, combined with oral therapy, is not considered here, as most of these studies are single studies and not widely practiced at this time [45–47]. However, support for adjunctive therapy, particularly in the more severe cases of onychomycosis, has increased, in an effort to improve cure rates without increasing exposure to oral medications [48]. Further studies of such combinations are anticipated.

We have not considered trials that used nonstandard regimens such as sequential or combination therapy (with the exception of combination of amorolfine and ciclopirox with oral therapies) and the trials using ketoconazole to treat onychomycosis, given the potential of this agent to cause hepatotoxicity and the availability of alternative agents.

## Questions

### What is the role of oral antifungal therapy in the management of dermatophyte onychomycosis in adults?

Griseofulvin was the first significant oral antifungal agent available for the management of dermatomycoses. Over the years, the use of griseofulvin in the treatment of onychomycosis has decreased, although it is still widely used for the treatment of tinea capitis [49]. Ketoconazole, an oral imidazole, is no longer recommended for the treatment of onychomycosis, which requires a long duration of therapy, due to the potential for hepatotoxicity [49]. The introduction of the new oral antifungal agents terbinafine, itraconazole, and fluconazole has led to improved efficacy rates, decreased treatment duration, and fewer adverse events.

The use of ravuconazole for the management of onychomycosis has not been considered further in this chapter, as only one published report of efficacy is known to us [27]. The treatment of onychomycosis with posaconazole is still under investigation [28].

### What are the effects of systemic treatments on fingernail and on toenail onychomycosis caused by dermatophytes in healthy adults?

#### Griseofulvin

The regimen for treating onychomycosis is continuous therapy using a dosage of 500 mg/day to 1 g/day, typically administered for 6–12 months in fingernail onychomycosis and for 9–18 months in toenail disease.

#### Fingernails (quality of evidence: 2)

One randomized double-blind study compared griseofulvin with terbinafine in the treatment of onychomycosis (Table 43.1) [50]. The methods used for generation of the randomization sequence and for the allocation concealment were not specified and a per-protocol analysis was performed with 20/92 (22%) of participants excluded.



**Table 43.1** Systemic treatments of dermatophyte fingernail onychomycosis.

Year	First author, ref.	Treat.	Study type	Sample size (n)	Regimen	Treat. duration	Follow-up period (from baseline)	Efficacy measure		
								MC <sup>a</sup>	CR <sup>b</sup>	CC <sup>c</sup>
1995	Haneke [50]	GRIS	DB, R, comparative	92	500 mg/day	12 wk, followed by 12 wk placebo	12 mo	45/72 (63%)	—	28/72 (39%)
1992	Goodfield [54]	TERC	DB, R, parallel group, placebo controlled	8	250 mg/day	12 wk	12 mo	5/7 (71%)	5/7 (71%)	—
1995	Haneke [50]	TERC	DB, R, comparative	88	250 mg/day	12 wk, followed by 12 wk placebo	12 mo	62/67 (92%)	—	51/67 (76%)
1996	Tosti [55]	TERC	Open, R, comparative	5	250 mg/day	2 mo	8 mo	5/5 (100%)	5/5 (100%)	5/5 (100%)
1997	Tausch [56]	TERC	DB, R	25 (6 & 12 wk)	250 mg/day	6 wk, followed by 6 wk placebo	12 mo	—	—	6/8 (75%)
1997	Tausch [56]	TERC	DB, R	25 (6 & 12 wk)	250 mg/day	12 wk	12 mo	—	—	10/14 (71%)
2011	TER package insert [57]	TERC	DB, R, placebo controlled	Not stated	250 mg/day	6 wk	6 mo	(79%)	—	(59%)
1996	Tosti [55]	TERP	Open, R, comparative	4	500 mg/day 1 wk/mo	2 mo	8 mo	4/4 (100%)	3/4 (75%)	3/4 (75%)
1998	Gupta [58]	ITRP	Meta-analysis	210	400 mg/day 1 wk/mo	2 mo	9 mo	87 ± 8 (SE)	89 ± 6 (SE)	—
1998	Gupta [58]	ITRP	Meta-analysis	217	400 mg/day 1 wk/mo	3 mo	9 mo	97 ± 1 (SE)	98 ± 1 (SE)	—
1998	Gupta [58]	ITRC	Meta-analysis	211	200 mg/day	6 wk	9 mo	86 ± 3% (SE)	90 ± 2% (SE)	—
1996	Montero-Gei [59]	FLUC	Open, single-arm	16	150 mg/wk	12–48 wk (mean 27 wk)	9–18 mo	14/15 (93 %)	15/16 (94%)	—
1998	Drake [60]	FLUC	DB, R, parallel, multicenter, placebo controlled	84	150 mg/wk	Up to 9 mo	Up to 15 mo	70/78 (90%)	62/78 (79%)	61/78 (78%)
1998	Drake [60]	FLUC	DB, R, parallel, multicenter, placebo controlled	87	300 mg/wk	Up to 9 mo	Up to 15 mo	66/73 (90%)	66/73 (90%)	61/73 (84%)
1998	Drake [60]	FLUC	DB, R, parallel, multicenter, placebo controlled	88	450 mg/wk	Up to 9 mo	Up to 15 mo	75/76 (99%)	70/76 (92%)	69/76 (91%)

CC, complete cure; CR, clinical response; DB, double-blind; FLUC, fluconazole; GRIS, griseofulvin; ITRC, itraconazole continuous; ITRP, itraconazole pulse; MC, mycological cure; mo, months; R, randomized; TER, terbinafine; TERC, terbinafine continuous; TERP, terbinafine pulse; Treat., treatment; wk, weeks.

<sup>a</sup>Mycological cure defined as negative microscopy and culture, unless indicated otherwise.

<sup>b</sup>Clinical response defined as cured or markedly improved, unless indicated otherwise.

<sup>c</sup>Complete cure defined as mycological and clinical cure or markedly improved, unless indicated otherwise.

### Fingernails: effectiveness

In a double-blind randomized controlled trial (RCT), griseofulvin was given at a dosage of 500 mg/day for 12 weeks. The mycological cure rate and complete cure rate were 63% and 39%, respectively [50].

### Toenails (quality of evidence: 2)

Three systematic reviews were identified. One systematic review (search date November 2002: three RCTs, 167 participants) used a meta-analysis method to calculate sample-size-weighted cure rates [51]. The three RCTs were double-blind with homogeneous dosing regimens and outcomes. The quality of the RCTs included was not assessed. The second systematic review (search date March 2000: eight RCTs, 319 participants) was associated with high variability in dosing regimen and efficacy outcomes and the results were not

pooled together [52]. No information was given about the blinding of the studies included, though the quality of the studies was assessed but not presented separately for the studies investigating griseofulvin. The last systematic review (search date 1999: four RCTs, one comparative study, 211 participants) also used a meta-analysis method to calculate sample-size-weighted cure rates [53]. Four studies were double blind and one was open. The dosing regimen varies from 500 to 1000 mg daily for 6–12 months. None of these systematic reviews specified the type of analysis (intention-to-treat or per protocol) used by the included studies.

### Toenails: effectiveness

In the RCTs included in the first meta-analysis, 500 or 1000 mg/day of griseofulvin was administered for 1 year to treat onychomycosis. The pooled mycological cure rate was 60 ± 6% [51]. The dosing

regimens used in the studies included in the second systematic review varied from 200 to 1000 mg/day for 6–18 months and the resulting mycological cure rates ranged from 0 to 69% [52]. In the last systematic review including 500 or 1000 mg/day for 6–12 months, the pooled mycological cure rate was  $41.1 \pm 20.4\%$  (standard error, SE) [53].

### Drawbacks

The use of griseofulvin may be associated with adverse events such as gastrointestinal upset, nausea, diarrhea, headache, central nervous system symptoms, and urticaria [49]. No drugs are contraindicated with griseofulvin, and few drug interactions are associated with griseofulvin therapy [49].

### Comments

Griseofulvin was the first systemic agent used to treat onychomycosis on a widespread basis. Currently, the newer oral agents (itraconazole, terbinafine, and fluconazole) have been found to be more effective than griseofulvin; the duration of active therapy is also shorter with the more recently introduced antimycotics [61,62]. Moreover, when griseofulvin is used to treat dermatophyte toenail onychomycosis, relapse rates may be higher (40–60%) [63] in comparison with the newer oral antifungal agents [35,57,64–66].

### Continuous terbinafine

The regimen for fingernail and toenail onychomycosis is 250 mg/day, administered for 6 weeks and 12 weeks, respectively.

#### Fingernails (quality of evidence: 2)

Five RCTs (four double-blind [50,54,56,57], one open [55]) evaluated patients with fingernail onychomycosis. Little information was available on the study presented in terbinafine's label information [57]. One study used a randomized block of four participants [56] and the other three studies did not specify their methods of randomization and allocation concealment. The sample sizes varied from five to 88 participants (Table 43.1). One study [55] reported the efficacy outcome for all randomized participants, whereas the other three studies reported data from per-protocol analysis and one of these studies [50] excluded 24% (21/88) of participants.

#### Fingernails: effectiveness

The studies used terbinafine 250 mg/day for 6 weeks [56,57], 8 weeks [55], and/or 12 weeks [5,50,56] (Table 43.1). Mycological cure was achieved in 79% of patients treated for 6 weeks, 100% for 8 weeks, and 71–92% of patients treated for 12 weeks, whereas complete cure was achieved in 59–75% (6 weeks) and 71–76% (12 weeks).

#### Toenails (quality of evidence: 2)

The efficacy of continuous terbinafine in the treatment of dermatophyte toenail onychomycosis was investigated by five meta-analyses. Two meta-analyses – search date November 2002: 18 RCTs, 993 participants; search date 1999: 19 RCTs, one open, 1393 (mycological), and 1371 (clinical) participants – presented sample-size-weighted cure rates. One review did not specify the individual characteristics of the included studies [51]. The other study included 15 double-blind studies and five open studies [53]. The other three meta-analyses included studies comparing directly continuous terbinafine with pulsed terbinafine (search date January 2011: nine studies (eight RCTs, one retrospective study), 1135 participants) [67], continuous itraconazole (search date March 2000: two RCTs,

501 participants) [52], or pulsed itraconazole (search date March 2008: eight RCTs, 1181 (terbinafine and itraconazole) participants) [68]. The meta-analysis comparing continuous and intermittent terbinafine included three open, two investigator-blinded, and four double-blinded studies (see Pulsed terbinafine, Toenails). The two RCTs included in the comparison between continuous terbinafine and continuous itraconazole were double-blind studies, whereas the comparison between continuous terbinafine and intermittent itraconazole included open and investigator-blinded studies. With the exception of one meta-analysis [67], it was not specified if the data from the studies included were from intention-to-treat or per-protocol analysis.

#### Toenails: effectiveness

A pooled mycological cure rate of  $76 \pm 3\%$  and  $77.2 \pm 4.0\%$  (SE) was obtained with terbinafine 250 mg/day for 12–16 weeks [51,53]. Studies using four different pulsed terbinafine regimens compared with a continuous dosing regimen (250 mg/day for 12–16 weeks) gave a risk ratio (RR) of 0.87 (95% confidence interval [CI], 0.80–0.96;  $P = 0.003$ ;  $n = 8$ ) for per-protocol analysis of mycological cure and 0.93 (95% CI, 0.76–1.13;  $P = 0.44$ ;  $n = 9$ ) for per-protocol analysis of complete cure [67]. Similar results were obtained with intention-to-treat analyses. Thus, the chance of getting a complete cure was similar between the two types of dosing regimens, whereas the pulsed regimen had only 13% less chance than the continuous regimen to result in a mycological cure. In contrast, continuous terbinafine (250 mg/day for 12–16 weeks) was clearly superior to pulsed itraconazole (400 mg/day for 1 week/month, 3–4 months) based on an odds ratio of 2.31 (95% CI, 1.76–3.03;  $P \leq 0.0001$ ;  $n = 8$ ) for mycological cure [68] and to continuous itraconazole (200 mg/day for 12 weeks) based on a risk difference of  $-0.23$  (95% CI,  $-0.15$  to  $-0.32$ ;  $n = 501$ ) for mycological cure [52].

### Drawbacks

The treatment of onychomycosis with terbinafine (continuous) is associated with a low frequency of adverse events [69,70]. These adverse events are generally mild to moderate in severity, and reversible. The most common adverse events involve the gastrointestinal tract, skin, and central nervous system. Only a small proportion of patients discontinue treatment with terbinafine. Pretreatment serum transaminase tests (alanine transaminase and aspartate transaminase) should be considered in all patients before terbinafine therapy is initiated [57]. Terbinafine is an inhibitor of the CYP450 2D6 isozyme, which includes tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers, class 1C antiarrhythmics, and monoamine oxidase inhibitors [57,71,72]. Caution should be used when terbinafine is given to patients using drugs metabolized by CYP 2D6, particularly those drugs with a narrow therapeutic window [57].

### Comments

Terbinafine is effective and safe for the treatment of onychomycosis. Terbinafine is an allylamine that inhibits squalene epoxidase, resulting in an accumulation of squalene and a deficiency of ergosterol. The accumulation of squalene may be associated with fungicidal action [73]. There is a substantial number of high-quality studies that demonstrate the effectiveness of terbinafine (continuous) in the treatment of toenail onychomycosis, and meta-analyses showed its superiority to both continuous and pulsed itraconazole [52,68]. Moreover, a recent meta-analysis comparing the long-term recurrences of toenail onychomycosis showed that continuous ter-

binafine was associated with less mycological recurrences than itraconazole (pulsed and continuous) [74].

### **Pulsed terbinafine**

In contrast to continuous terbinafine, various dosing regimens have been used for intermittent terbinafine therapy.

#### ***Fingernails (quality of evidence: 2)***

Treatment of dermatophyte onychomycosis in fingernails with intermittent regimen of terbinafine has been investigated in three RCTs [55,75,76]. Only one open RCT reported separately the efficacy outcome for toenails and fingernails [55]. The participants were sequentially assigned to one of the three arms of this study and there was no drop out in the participants with fingernail onychomycosis in the intermittent terbinafine arm.

#### ***Fingernails: effectiveness***

Only four out of 21 participants randomized to the pulsed terbinafine had both fingernail and toenail onychomycosis and were treated with terbinafine 500 mg/day for 1 week per month for 4 months. All participants had mycological cure, but 75% (3/4) had complete cure of the fingernails (Table 43.1) [55].

#### ***Toenails (quality of evidence: 2)***

To our knowledge, four different pulse regimens have been investigated in clinical trials for terbinafine. These four regimens were analyzed in a subgroup meta-analysis including studies comparing directly continuous terbinafine with pulsed terbinafine (search date January 2011: nine studies (eight RCTs, one retrospective study), 1182 participants) [67]. Two investigator-blinded studies used two pulses of 250 mg/day for 4 weeks on and 4 weeks off [77,78]. Two double-blind studies used three pulses of 350 mg/day for 2 weeks on and 2 weeks off [79]. One open study and one double-blind study used three pulses of 500 mg/day for 1 week on and 3 weeks off [80,81]. Two open studies and one double-blind study used four pulses of 500 mg/day for 1 week on and 3 weeks off [55,82,83]. Separate analyses were performed for intention-to-treat and per-protocol data.

#### ***Toenails: effectiveness***

When all pulse regimens were pooled together, the efficacy of the pulse regimen was slightly inferior to the continuous terbinafine for mycological cure, but not for complete cure (see Continuous terbinafine/Toenails: effectiveness). Based on per-protocol analysis of RRs for mycological and complete cures, three pulses of terbinafine 350 mg/day for 2 weeks on/2 weeks off or 500 mg/day for 1 week on/3 weeks off were less effective than two pulses of 250 mg/day for 4 weeks on/4 weeks off or four pulses of 500 mg/day for 1 week on /3 weeks off when compared with continuous terbinafine [67].

### **Drawbacks**

Intermittent terbinafine therapy has been associated with few adverse events. Adverse events are generally mild to moderate, and reversible. The spectrum of adverse effects is similar to that seen with the continuous terbinafine regimen [78–82]. A terbinafine (pulse) regimen is not indicated for the treatment of onychomycosis, and therefore there are no monitoring guidelines in the USA.

### **Comments**

The preferred regimen for the treatment of onychomycosis using terbinafine is continuous rather than pulse therapy. Moreover, there

is no evidence so far that an intermittent terbinafine therapy might be more advantageous in terms of cost, compliance, adverse events, or fungal resistance [67].

### **Pulse itraconazole**

Itraconazole pulse therapy is taken to be 200 mg twice a day for 1 week, followed by 3 weeks off between successive pulses. Typically, two pulses are administered for fingernail onychomycosis and three or four pulses for toenail disease. Pulse dosing is the regimen approved by the Food and Drugs Administration (FDA) regimen for infections of the fingernails when no toenail involvement has been noted [66].

#### ***Fingernails (quality of evidence: 2)***

The efficacy of intermittent itraconazole in the treatment of dermatophyte fingernail onychomycosis was investigated in one meta-analysis [58]. This meta-analysis (search date before 1998: 210 (two pulses) and 217 (three pulses) participants) presented sample-size-weighted cure rates without specifying the individual characteristics of the studies included (Table 43.1).

#### ***Fingernails: effectiveness***

Itraconazole was given 400 mg/day for 1 week per month for 2 or 3 months. The mycological cure rates obtained were  $87 \pm 8\%$  (SE) and  $97 \pm 1\%$  and the clinical response rates were  $89 \pm 6\%$  and  $98 \pm 1\%$ , respectively (Table 43.1).

#### ***Toenails (quality of evidence: 2)***

The efficacy of intermittent itraconazole in the treatment of dermatophyte toenail onychomycosis was investigated in four meta-analyses. Two meta-analyses – search date November 2002: six RCTs, 318 (mycological) and 329 (clinical) participants [51]; search date before 1998: 1389 (three pulses) or 259 (four pulses) participants [58] – presented sample-size-weighted cure rates without specifying the individual characteristics of the studies included. The third meta-analysis (search date 1999: six RCTs, five open studies, 1486 (mycological) or 1610 (clinical) participants) also presented sample-size-weighted cure rates and included four double-blind studies and seven open studies [53]. The last meta-analysis included studies comparing directly pulsed itraconazole with continuous terbinafine (search date March 2008: eight RCTs, 1181 (terbinafine and itraconazole) participants) [68]. No systematic review was found for comparison between pulsed and continuous itraconazole, but one double-blind placebo-controlled RCT investigated the efficacy of the two dosing regimens for toenail onychomycosis only [84]. Three of the 65 participants (4.6%) in the continuous itraconazole group and five of the 64 participants (7.8%) in the pulsed itraconazole group discontinued or were excluded from the study. The type of analysis used for the efficacy data was not explicitly stated.

#### ***Toenails: effectiveness***

In the earliest meta-analysis, similar pooled mycological cure rates were obtained for three ( $77 \pm 5\%$  (SE)) and four ( $78 \pm 4\%$ ) pulses, but not for clinical response rates (three pulses:  $82 \pm 3\%$ ; four pulses:  $92 \pm 3\%$ ) [58]. A mycological cure rates of  $63 \pm 7\%$ , and  $70.8 \pm 5.7\%$  (SE) and a clinical response (cure or markedly improved) rates of  $70 \pm 11\%$  and  $73.6 \pm 4.6\%$  (SE) were obtained when pooling the results from studies using itraconazole 400 mg/day 1 week per month for 3–4 months [51,53]. As previously mentioned in the section on terbinafine, intermittent itraconazole

therapy with the same dosing regimen has been shown to be inferior to continuous terbinafine regimen for both mycological and clinical cures [68]. No difference in mycological or clinical cure was observed at 12-month follow-up after 3 months of pulsed itraconazole (400 mg/day, 1 week per month) and 3 months of continuous itraconazole (200 mg/day) [84].

### Drawbacks

Itraconazole (pulse) therapy is approved for fingernail, but not toenail, onychomycosis in the USA [66]. Adverse events occur with a low frequency and are generally mild to moderate in severity, and reversible. These events include gastrointestinal upset, cutaneous eruption, and headache [58]. Studies report a low discontinuation rate due to an adverse event. Itraconazole has the potential for numerous drug interactions, and a thorough review of current medications being used by the patient is required before prescribing [66,71,72,85]. In some cases, the drug interaction may be explained on the basis of an inhibition of cytochrome P450 3A4 by itraconazole. Itraconazole is contraindicated with cisapride, pimozide, quinidine, dofetilide, and levacetylmethadol (levomethadyl) [66,85]. Itraconazole is contraindicated in the USA and Canada in patients with evidence of ventricular dysfunction – for example, congestive heart failure or a history of heart failure [66]. Liver function monitoring should be done in patients with preexisting hepatic function abnormalities or a history of liver toxicity with a previous medication, and should be considered for all patients using itraconazole [66].

### Comments

Itraconazole pulse therapy is effective and safe in onychomycosis. The pulse regimen used to treat toenail onychomycosis decreases the itraconazole required by one-half in comparison with the continuous regimen with this triazole. This may result in cost savings and increased compliance and may reduce the frequency of adverse events [58,86–89]. In fact, the pulse regimen is the preferred mode of drug delivery when using itraconazole. No significant difference was found between three-pulse and four-pulse regimens of itraconazole for the primary efficacy parameters in the treatment of toenail onychomycosis [90]. As previously mentioned, a recent meta-analysis of comparing the long-term recurrences of toenail onychomycosis showed that itraconazole therapy (pulsed and continuous) was associated with more mycological recurrences than continuous terbinafine [74].

### Continuous itraconazole

The regimen for fingernail and toenail onychomycosis is 200 mg/day administered for 6 weeks and 12 weeks, respectively. Continuous itraconazole is used infrequently in current practice, in favor of the pulse itraconazole regimen.

### Fingernails (quality of evidence: 2)

No RCTs have been published on the use of continuous itraconazole for fingernail onychomycosis only. A meta-analysis of early clinical trials with similar protocols (search date before 1998: eight studies (five placebo controlled, three open studies),  $n = 211$  participants) used a modified Der Simonian and Laird method for single group analysis [58]. No further details were given on the individual studies.

### Fingernails: effectiveness

Pooled mycological and clinical response rates of  $86 \pm 3\%$  (SE) and  $90 \pm 2\%$  (SE) were obtained with itraconazole therapy of 200 mg/day for 6 weeks (Table 43.1) [58].

### Toenails (quality of evidence: 2)

Efficacy of continuous itraconazole for toenail onychomycosis was investigated in four meta-analyses. Two meta-analyses – search date November 2002: seven RCTs, 1131 participants [51]; search date before 1998: 20 studies (five placebo controlled, six comparative, nine open), 1741 participants [58] – presented sample-size-weighted cure rates without specifying the individual characteristics of the studies included. The third meta-analysis (search date 1999: 12 RCTs, 1562 participants) also calculated sample-size-weighted cure rates and included 10 double-blind studies, one open study, and one study with no specified blinding [53]. The last meta-analysis included studies comparing directly continuous itraconazole and continuous terbinafine (search date March 2000: two RCTs, 501 (itraconazole and terbinafine) participants) [52]. As previously mentioned for the intermittent itraconazole regimen, no systemic review was found for comparison between pulsed and continuous itraconazole, but one double-blind placebo-controlled RCT investigated the efficacy of the two dosing regimens for toenail onychomycosis only [84].

### Toenails: effectiveness

In the earliest meta-analysis, a pooled mycological cure rate of  $74 \pm 3\%$  (SE) was obtained with 200 mg/day itraconazole for 3 months [58]. A pooled mycological cure rate of  $59 \pm 5\%$  and  $66.3 \pm 4.2\%$  (SE) was obtained for itraconazole 200 mg/day for 3–4 months [51,53]. Itraconazole 200 mg/day for 3 months was found to be as effective as pulsed itraconazole (see Pulse itraconazole/Toenails: effectiveness), but less effective than continuous terbinafine (see Continuous terbinafine/Toenails: effectiveness).

### Drawbacks

Adverse events associated with the use of continuous itraconazole for the treatment of onychomycosis are not common, and those experienced are generally mild to moderate in severity. Adverse events include gastrointestinal disorders (e.g., nausea, abdominal pain), rashes, and central nervous system effects (e.g., headache) [58,84,87–89]. Only a small proportion of patients discontinue treatment with the triazole. There are drugs that are contraindicated with itraconazole (see Pulse itraconazole/Drawbacks). In addition, the triazole has several drug interactions (see Pulse itraconazole/Drawbacks). Itraconazole is contraindicated in North America in patients with evidence of ventricular dysfunction – for example, congestive heart failure or a history of heart failure. The US package insert suggests that liver function tests should be considered for all patients receiving continuous therapy [66]. Treatment should be stopped immediately and liver function tests should be performed whenever a patient develops signs and symptoms suggestive of liver disease [66].

### Comments

Continuous itraconazole therapy is an effective and well-tolerated treatment for onychomycosis. Historically, the treatment of onychomycosis with itraconazole was with the continuous regimen; later, work done by de Doncker *et al.* [89,90] resulted in the widespread adaptation of pulse therapy for this indication. The US package insert states that when patients with toenail onychomycosis were treated with itraconazole continuous therapy, 21% of the overall success group had a relapse (worsening of the global score or conversion of KOH or culture from negative to positive) [66].

### Fluconazole

Various fluconazole weekly dosing regimens have been used for dermatophyte onychomycosis. The dosage varied from 150 mg/



week to 450 mg/week and the duration from 12 to 48 weeks. A recent systematic review showed that the efficacy was not improved by increasing the fluconazole dose but a better efficacy was obtained with treatment longer than 6 months [91]. Consequently, 150 mg of fluconazole weekly for more than 24 weeks is recommended, and the evidence for this dosing regimen (150–450 mg) longer than 6 months will be presented in the following sections.

### **Fingernails (quality of evidence: 2)**

A systematic review (search date January 2012: two studies (one RCT, one nonrandomized),  $n = 243$  participants) presented cure rates for per-protocol analysis [91]. The two studies included are presented in Table 43.1. The RCT was double blind and placebo controlled [60] and the open nonrandomized study included both fingernail and toenail onychomycosis [59].

### **Fingernails: effectiveness**

The mycological cure rates obtained for 150–450 mg fluconazole administered weekly vary from 90 to 99% and the complete cure rates vary from 78 to 91% (Table 43.1).

### **Toenails (quality of evidence: 2)**

Two systematic reviews investigated the efficacy of fluconazole for toenail onychomycosis caused by dermatophytes. The first review (search date 1999: four studies (two RCTs, two open), 288 (mycological) or 292 (clinical) participants) calculated sample-size-weighted cure rates and included two double-blind studies and two open studies [53]. The other systematic review (search date January 2012: four studies (three RCTs, one nonrandomized),  $n = 590$  participants) calculated unweighted mean cure rates obtained for per-protocol analysis [91]. The three RCTs were double blind and placebo controlled, and the open nonrandomized study presented separately data for fingernail and toenail onychomycosis.

### **Toenails: effectiveness**

A mean mycological cure rate of  $61.7 \pm 8.1\%$  (standard deviation, SD) and a mean clinical cure rate of  $46.7 \pm 11.9\%$  were obtained with fluconazole therapy of 150–450 mg weekly for more than 24 weeks [91]. A pooled mycological rate of  $65.6 \pm 7.1\%$  (SE) and a pooled clinical response (cure or markedly improved) rate of  $66.5 \pm 11.7\%$  (SE) were obtained with 150 mg weekly for 3–12 months [53].

### **Drawbacks**

Fluconazole is not approved for the treatment of onychomycosis in North America. The more common adverse effects observed with fluconazole affect the gastrointestinal tract, cutaneous system, and central nervous system [72,92]. Adverse events do not commonly occur, and those experienced are usually of mild to moderate severity and reversible. Only a small proportion of patients discontinue treatment with fluconazole. The drugs contraindicated with fluconazole are cisapride and terfenadine. There are some drug interactions that may occur with the triazole; in certain cases, the drug interactions may be explained by fluconazole inhibiting cytochrome P450 2C9, and at higher doses the triazole may inhibit cytochrome P450 3A4 [71,72].

### **Comments**

Fluconazole is effective and safe in onychomycosis. In comparison with terbinafine and itraconazole, there are relatively few studies that have evaluated the efficacy of fluconazole in the treatment of

toenail onychomycosis. The preferred regimen for fluconazole is once-weekly therapy; typically, 150 mg per week administered for more than 6 months. In the study reported by Scher *et al.*, the clinical relapse rate over a 6-month follow-up was 4.4% [36].

### **Posaconazole**

Four dosing regimens of an oral suspension of posaconazole have been investigated for the treatment of toenail onychomycosis caused by dermatophytes: 100 mg/day for 24 weeks, 200 mg/day for 24 weeks, 400 mg/day for 12 weeks, and 400 mg/day for 24 weeks. Higher efficacy was obtained with 200 mg and 400 mg daily for 24 weeks [28].

### **Fingernails (quality of evidence: no evidence found)**

There was no publication on the efficacy of posaconazole therapy for fingernail onychomycosis.

### **Toenails: (quality of evidence: 2)**

One RCT compared four different regimens of posaconazole with terbinafine (250 mg/day for 12 weeks, investigator blinded) and placebo (double blind) [28]. The participants were randomized according to a computer-generated randomization schedule using a central interactive voice response system. An intention-to-treat analysis (modified and unmodified) was used for the primary efficacy outcome, but the study had small sample sizes.

### **Toenails: effectiveness**

At week 48 assessment, the mycological cure rates were respectively 70% (26/37) and 79% (26/33) for 200 mg and 400 mg for 24 weeks. The corresponding complete cure rates were 54% (20/37) and 46% (15/33). These rates were obtained based on modified intention-to-treat analysis including randomized participants who received at least one dose of posaconazole and with one postbaseline assessment.

### **Drawbacks**

Posaconazole is approved for the prophylaxis of invasive *Aspergillus* and *Candida* infections and the treatment of oropharyngeal candidiasis, but not for onychomycosis [93]. The adverse events observed during treatment of onychomycosis were mild to moderate in severity. The most commonly reported treatment-related adverse events were diarrhea (5%), nausea (4%), dizziness (4%), and headache (6%). A small proportion of patients (4%) discontinue treatment with posaconazole because of adverse events [28]. The drugs contraindicated with posaconazole are sirolimus, CYP3A4 substrates such as pimozide and quinidine, simvastatin, and ergot alkaloids [93].

### **Comments**

The higher concentration of 400 mg did not result in higher efficacy compared with the 200 mg regimen. The regimens of 200 and 400 mg posaconazole daily for 24 weeks had similar mycological cure rates and numerically, but not statistically, higher complete cure rates compared with the terbinafine arm included in the study (250 mg daily for 12 weeks; mycological: 71%; complete: 36%). However, when administered only for 12 weeks, 400 mg/day posaconazole was clearly inferior to terbinafine for the same therapy duration (mycological: 43%; complete: 20%) [28]. Thus, the duration of the posaconazole therapy must be much longer to be as effective as terbinafine. This is consistent with their *in vitro*

antifungal activities for dermatophytes [94]. In contrast, posaconazole had been shown to be more effective than terbinafine in vitro for non-dermatophyte molds and yeasts [94], but the efficacy of posaconazole therapy for the treatment of onychomycosis caused by these agents has not been investigated yet.

### **What are the effects of topical nail lacquers on toenail onychomycosis?**

Nail lacquers provide a direct application of antifungal medication, with the lacquer formulation providing a stable matrix of concentrated medication that aids drug penetration. Topical medications are associated with fewer and less severe adverse events than oral medications, and with less potential for drug interaction than use of oral antifungals. These make topical lacquers a desirable mode of antifungal treatment.

#### **Amorolfine nail lacquer**

Amorolfine 5% nail lacquer can be used once or twice weekly for 6 months for toenail onychomycosis.

#### **Quality of evidence: 2**

One randomized study reporting cure rates investigated amorolfine lacquer therapy for fingernail and/or toenail onychomycosis caused by dermatophytes only. This study was an open study comparing once-weekly versus twice-weekly application of the nail lacquer [95]. Per-protocol results were presented and 42% (169/405) of the participants were not included in the analysis (Table 43.2).

#### **Effectiveness**

Follow-up at 3 months posttreatment (month 9 of the study) showed mycological and complete cure rates of 77% and 47%, respectively (Table 43.2).

#### **Drawbacks**

The patients should have no matrix involvement [102]. No further research has been reported on the use of amorolfine monotherapy.

#### **Comments**

Amorolfine has few safety concerns in comparison with oral therapy, with mild topical irritation being the most prevalent event. One patient who inadvertently used amorolfine twice daily rather than twice weekly reported no irritation [103]. Amorolfine may be an effective treatment for patients with milder, nonmatrix onychomycosis. Amorolfine nail lacquer once every 2 weeks has also been successfully used to prevent onychomycosis recurrence [104].

#### **Amorolfine nail lacquer combined with oral antifungal therapy**

Five trials have used amorolfine in combination with oral antifungals: one using continuous griseofulvin [96], three using continuous terbinafine [75,97,98], and one using continuous itraconazole [99]. All trials involved onychomycosis with matrix involvement.

#### **Amorolfine with griseofulvin (quality of evidence: 2)**

One open randomized study compared combined amorolfine nail lacquer and shorter griseofulvin therapy and longer monotherapy with griseofulvin [96]. Results from per-protocol analysis were presented and 32% (29/91) and 45% (41/91) of the participants were excluded of the analysis for the combined therapy and griseofulvin-only groups (Table 43.2).

#### **Amorolfine with griseofulvin: effectiveness**

Two months of twice-daily griseofulvin combined with twice-weekly amorolfine for 12 months resulted in similar mycological and clinical cures as 12 months of continuous griseofulvin therapy (twice daily for 2 months and once daily for the following 10 months) (Table 43.1).

#### **Amorolfine with terbinafine (quality of evidence: 2)**

Three RCTs investigated the efficacy of 5% amorolfine nail lacquer combined with systemic terbinafine compared with monotherapy with terbinafine for dermatophyte onychomycosis. Two studies were open, included participants with toenail onychomycosis only, and presented results from intention-to-treat analysis [97,98], whereas the other study was also open but included both fingernail and toenail onychomycosis and presented data from per-protocol analysis [75]. This latter study included participants with onychomycosis caused by dermatophytes, non-dermatophyte molds, and yeasts and did not specify the number of participants with confirmed dermatophyte onychomycosis randomized to the three arms of the study by using a table of random numbers.

#### **Amorolfine with terbinafine: effectiveness**

Complete cure rates obtained for continuous terbinafine for 12 weeks combined with 15 months of weekly application of 5% amorolfine nail lacquer (59–72%) were superior to the complete cure rates obtained with the terbinafine monotherapy for 12 weeks (38–45%) for the treatment of toenails (Table 43.2) [97,98]. Weekly amorolfine nail lacquer combined with pulse terbinafine (500 mg daily for 1 week per month) for 4 months resulted in a similar mycological cure rate (86%) to the pulse terbinafine monotherapy (89%) for fingernail/toenail dermatophyte onychomycosis (Table 43.2) [75].

#### **Amorolfine with itraconazole (quality of evidence: 2)**

There was no study reporting efficacy data for onychomycosis caused by dermatophytes only. However, one open RCT with 75% of participants with toenail onychomycosis caused by dermatophytes compared continuous itraconazole therapy with and without amorolfine nail lacquer [99]. Results from per-protocol analysis were presented, but statistical analyses were performed and significant for both per-protocol and intention-to-treat analyses. More participants were excluded from the per-protocol analysis in the itraconazole + placebo group (11/43 = 26%) than the two itraconazole + amorolfine arms (8/51 = 16% and 4/37 = 11%) (Table 43.2).

#### **Amorolfine with itraconazole: effectiveness**

Combined use of amorolfine once weekly for 24 weeks with continuous itraconazole for 12 weeks showed a complete cure rate at week 24 of 94%, versus 69% for continuous itraconazole alone [99].

#### **Drawbacks**

The open design may produce some bias in assessment. Blinded studies should be done to confirm the results. There was a relatively high drop-out rate, with many patients leaving due to lack of efficacy.

#### **Comments**

The rate and type of adverse events noted with combination therapies were similar to those noted with the respective monotherapies. Combination therapy may increase efficacy, but further blinded

**Table 43.2** Treatment of onychomycosis with nail lacquers as monotherapy or in combination with oral antifungals.

Year	First author, ref.	Treatment	Study type	Sample size (n)	Regimen	Treatment duration	Follow-up period (from baseline)	Efficacy measure		
								MC <sup>a</sup>	CR <sup>b</sup>	CC <sup>c</sup>
1992	Reinel [95]	AMOR	R, open, multicenter	405 (dermatophytes)	Once or twice weekly	6 mo	9 mo	181/236 (77%)	—	112/236 (47%)
1995	Zaug [96]	AMOR + 500 mg GRIS	R, open, comparative	91	AMOR: twice weekly	AMOR: 12 mo	15 mo	39/62 (63%)	28/62 (45%)	—
					GRIS: twice daily	GRIS: 2 mo				
		500 mg GRIS		103	GRIS: (1) twice daily	GRIS: (1) first 2 mo	15 mo	31/62 (50%)	26/62 (42%)	—
					(2) once daily	(2) following 10 mo				
2000	Baran [97]	AMOR + 250 mg TER	R, open, comparative	(1) 50 (2) 48	AMOR: weekly	AMOR: 15 mo	18 mo	—	—	(1) 22/50 (44%) (2) 34/47 (72%)
					TER: daily	TER: (1) 6 wk (2) 12 wk				
		250 mg TER		49	TER: daily	TER: 12 wk	18 mo	—	—	18/48 (38%)
2007	Baran [98]	AMOR + 250 mg TER	R, open, multicenter, comparative	120	AMOR: weekly	AMOR: 12 mo	18 mo	—	—	71/120 (59%)
		250 mg TER		129	TER: daily	TER: 3 mo	18 mo	—	—	58/129 (45%)
2007	Jaiswal [75]	AMOR + 250 mg TER	R, open, comparative	Not given for dermatophyte	AMOR: weekly TER: twice daily for 1 wk/mo	4 mo	9 mo	6/7 (86%)	—	—
		250 mg TER			TER: twice daily for 1 wk/mo	4 mo	9 mo	16/18 (89%)	—	—
2002	Lecha [99]	AMOR + 200 mg ITRA	R, open, multicenter, comparative	(1) 51 (2) 37	AMOR: weekly	AMOR: 24 wk	6 mo	—	—	(1) 36/43 (84%) (2) 31/33 (94%)
		200 mg ITRA		43	ITRA: daily	ITRA: (1) 6 wk (2) 12 wk				22/32 (69%)
2000	Gupta [53]	CICL	Meta-analysis of 10 studies	2027 [MC] 2174 [CR]	Daily (9 studies) 3/2/1 (1 study)	12–48 wk	At least 6 mo	52.6 ± 4.2% (SE)	52.4 ± 9.0% (SE)	—
2009	Baran [100]	(1) P-3051 CICL (2) CICL	R, SB, multicenter, placebo controlled, comparative	(1) 182 (2) 188	Daily	48 wk	15 mo	—	—	(1) 20/157 (13%) (2) 9/156 (6%)
2005	Avner [101]	CICL + 250 mg TER	R, comparative	(80 randomized between 2 arms)	CICL: daily	CICL: 9 mo	9 mo	30/34 (88%)	28/34 (82%)	23/34 (68%)
		250 mg TER			TER: daily	TER: 4 mo	9 mo	22/34 (65%)	20/34 (59%)	17/34 (50%)
2005	Gupta [77]	CICL + 250 mg TER	R, SB, multicenter, comparative	(1) 21 (2) 27	CICL: daily	CICL: 48 wk	12 mo	(1) 14/21 (67%) (2) 19/27 (70%)	(1) 9/20 (45%) (2) 9/24 (38%)	(1) 8/20 (40%) <sup>d</sup> (2) 8/24 (33%) <sup>d</sup>
					TER: daily	TER: (1) 4 wk on, 4 wk off, 4 wk on (2) 12 wk				

Continued

Table 43.2 Continued

Year	First author, ref.	Treatment	Study type	Sample size (n)	Regimen	Treatment duration	Follow-up period (from baseline)	Efficacy measure		
								MC <sup>a</sup>	CR <sup>b</sup>	CC <sup>c</sup>
		250 mg TER		25	TER: daily	12 wk		14/25 (56%)	10/23 (44%)	8/23 (35%) <sup>d</sup>
2007	Jaiswal [75]	CICL + 250 mg TER	R, open, comparative	Not given for dermatophyte	CICL: daily TER: twice daily for 1 wk/mo	4 mo	9 mo	8/9 (89%)	—	—

3/2/1, 3 days/week for first month, 2 days/week for the second month, and 1 day/week for the other months; AMOR, amorolfine 5% nail lacquer; CC, complete cure; CICL, ciclopirox 8% nail lacquer; CR, clinical response; DB, double-blind; GRIS, griseofulvin, ITRA: itraconazole; MC, mycological cure; mo, months; R, randomized; SB, single-blind; SE, standard error, TER, terbinafine; wk, weeks.

<sup>a</sup>Mycological cure defined as negative microscopy and culture, unless indicated otherwise.

<sup>b</sup>Clinical response defined as cured or markedly improved, unless indicated otherwise.

<sup>c</sup>Complete cure defined as mycological and clinical cure or markedly improvement, unless indicated otherwise.

<sup>d</sup>Effective cure defined as mycological and >90% reduction in the disease area from baseline.

trials should be carried out to investigate combination therapy with amorolfine.

### Ciclopirox 8% nail lacquer

Ciclopirox 8% nail lacquer is recommended for use once daily for 48 weeks in mild to moderate onychomycosis. This is the first topical therapy to be approved for use in onychomycosis in the USA and Canada.

#### Fingernails (quality of evidence: no evidence found)

Studies investigating ciclopirox nail lacquer treatment for fingernail onychomycosis were not found.

#### Toenails (quality of evidence: 2)

One meta-analysis (search date 1999: 10 studies (two RCTs, eight open), 2027 (mycological) or 2174 (clinical) participants) was identified. This meta-analysis calculated sample-size-weighted cure rates and included two double-blind and eight open studies [53]. The results from one investigator-blinded RCT comparing the traditional 8% ciclopirox formulation with a new formulation (P-3051) are also presented [100]. In this placebo-controlled study, the participants were randomized by using an uneven block of five for the three study arms and a per-protocol analysis was performed (Table 43.2).

#### Toenails: effectiveness

The pooled mycological cure rate was  $52.6 \pm 4.2\%$  (SE) and the clinical response (cure or markedly improved) rate was  $52.4 \pm 9.0\%$  (SE) (Table 43.2) [53]. A better complete cure rate was obtained with the new formulation (13%) compared with the traditional formulation (6%) (Table 43.2) [100].

#### Drawbacks

Further data on the use of ciclopirox for the treatment of dermatophyte onychomycosis in blinded trials are needed.

#### Comments

Adverse events were noted rarely with ciclopirox use [105]. Most reactions were localized to the application site, mild in intensity, and transient. No serious adverse events were reported. Two open-label studies have showed clinical improvement with ciclopirox

therapy for 63–89% of onychomycosis patients with diabetes [106,107].

### Ciclopirox 8% nail lacquer combined with oral antifungal therapy

#### Ciclopirox with terbinafine: (quality of evidence: 2)

Three RCTs comparing monotherapy for terbinafine and combined therapy with ciclopirox nail lacquer for treatment of dermatophyte onychomycosis were identified. Two studies included participants with infected fingernails and/or toenails [75,101], and one study included participants with infected toenails [77]. The blinding and randomization methods were not specified for one study [101]. One study was open and used a table of random numbers for the participants' randomization [75], and the last study was investigator blind and used a predetermined randomization schedule [77]. Per-protocol analysis was generally used with the exception of the mycological cure rates reported in the investigator-blinded study.

#### Ciclopirox with terbinafine: effectiveness

Both continuous [77,101] and pulse [75,77] terbinafine regimens have been combined with ciclopirox nail lacquer. Combination of ciclopirox applied daily for 9 months and terbinafine daily for 4 months resulted in higher mycological cure (88% vs 65%), clinical response (82% vs 59%), and complete cure (68% vs 50%) compared with daily terbinafine for 4 months (Table 43.2) [101]. Longer therapy with daily ciclopirox daily (48 weeks) combined with shorter daily terbinafine therapy (3 months) resulted in higher mycological cure (70% vs 56%), but comparable clinical response (38% vs 44%) or effective cure (33% vs 35%) than 3 months of daily terbinafine only (Table 43.2) [77]. In the same study, a pulse terbinafine regimen (daily for 4 weeks on, 4 weeks off, and 4 weeks on) combined with daily ciclopirox for 48 weeks resulted in similar cure rates to the continuous regimen (Table 43.2). A similar mycological cure rate was also observed with pulse terbinafine (500 mg daily for 1 week per month for 4 months) with (89%) and without (89%) ciclopirox nail lacquer daily for 4 months (Table 43.2) [75].

#### Drawbacks

The number of patients in each study is relatively low. Further blinded trials are needed in order to increase the data available on



the use of ciclopirox in combination with oral antifungals to determine if combination therapy would result in higher efficacy.

### Comments

Most adverse events possibly related to study medication in the blinded trial were minimal and evenly distributed between the treatment groups [77].

## What are the effects of device-based therapies on toenail onychomycosis?

### Laser device systems

Laser device systems use photoselective effects to kill the fungal infection in the nail plate, so that new nail growth can replace the infected portion of the nail plate.

### Toenails (quality of evidence: 2)

One double-blind RCT was found for the treatment of onychomycosis with lasers (Table 43.3) [108,109]. The patients received treatment or sham and the clinical outcome was assessed by both an unblinded investigator and a blinded panel. The efficacy outcomes were presented for treated nails, not for the randomized partici-

pants. Several single-assignment open-label studies have also been conducted on neodymium-yttrium-aluminum garnet (Nd:YAG) and diode laser device systems with various laser models and treatment paradigms (Table 43.3) [110–116].

### Toenails: effectiveness

There was a lot of variability in the definition of the efficacy outcomes presented in the studies (Table 43.3). Cure rates were presented as per patients or per-treated nails. The exact definition of the mycological cure was not always given, but it was generally defined as negative culture. A low mycological cure rate of 50–59% of the nails was obtained in the RCT compared with the other studies, where up to 100% of the patients were cured. A rate for clinical response of 8% of the treated nails was obtained in the RCT. Complete cure rates were higher at 6-month follow-up (39–51% of the treated nails) compared with 9-month follow-up (8%).

### Drawbacks

Laser device systems are new technology and the studies conducted thus far have been limited in terms of sample size and methodology. Owing to the limited duration of the follow-up periods

**Table 43.3** Laser therapies for toenail onychomycosis.

Year	First author, ref.	Treatment	Study type	Patients (n)	Regimen	Treatment duration	Follow-up period (from baseline)	Efficacy measure		
								MC	CR	CC
2009	Harris [110]	Nd:YAG laser, 1064 nm	Single assignment, open	17	2.5 mm spot	1 visit	6 months	—	—	—
2010	Kozarev [111]	Nd:YAG laser, 1064 nm	Single assignment, open	72	35 ms pulse duration, 1 Hz, 4 mm spot size, 35–40 J/cm <sup>2</sup> , 4 tx at 1 week intervals	1 month	12 months	100% <sup>a</sup>	—	—
2010 2012	Landsman [108] Landsman [109]	Diode, 870 and 930 nm	Randomized, double blind, no treatment controlled	26	4 min at 870 and 930 nm, 15 mm spot size, 424 J/cm <sup>2</sup> and 2 min at 870 and 930 nm, 150 mm spot size, 204 J/cm <sup>2</sup> ; 4 tx at 1, 14, 42, and 120 days	4 months	6 months	50% <sup>a</sup> (nails)	8% <sup>c</sup> (nails)	39% <sup>d</sup> (nails)
							9 months	59% <sup>a</sup> (nails) 38% <sup>b</sup> (nails)	—	8% <sup>a</sup> (nails)
2011	Kozarev [112]	Nd:YAG laser, 1064 nm	Single assignment, open	162	35 ms pulse duration, 1 Hz, 4 mm spot size, 35–40 J/cm <sup>2</sup> , 4 tx at 1 week intervals	1 month	12 months	100%	—	—
2011	Weiss [113]	Nd:YAG laser, 1064 nm	Single assignment, open	7	0.3 ms pulse, 2 Hz, 5 mm spot size, 16 J/cm <sup>2</sup> , 2 tx at 6 week intervals	3 months	3 months	—	—	—
2011	Hochman [114]	Nd:YAG laser, 1064 nm	Single assignment, open	8	0.65 ms pulse, 2 mm spot size, 223 J/cm <sup>2</sup> , 2 or 3 tx at 3 week intervals	6–9 weeks	4–6 months after last tx	87.5% <sup>a</sup>	—	—
2012	Waibel [115]	Nd:YAG laser, 1064 nm	Single assignment, open	21	0.3 ms pulse, 5 Hz, 14 J/cm <sup>2</sup> , 5 mm spot size, 4 tx at 1 week intervals	1 month	6 months	95%	—	—
2012	Kimura [116]	Nd:YAG laser, 1064 nm	Single assignment, open	13	0.3 ms pulse, 5 Hz, 14 J/cm <sup>2</sup> , 5 mm spot size, 1–3 treatments at 4 or 8 week intervals	Varied	6 months	—	—	51% <sup>f</sup> (nails)

CC, complete cure; CR, clinical response; MC, mycological cure; tx, treatment.

<sup>a</sup>Negative culture.

<sup>b</sup>Negative culture and periodic acid and Schiff staining.

<sup>c</sup>Markedly improved or completely cleared.

<sup>d</sup>Negative culture with at least 3 mm of clear nail growth.

<sup>e</sup>Clinical cure with mycological cure.

<sup>f</sup>Clear nail with negative microscopy.

posttreatment, we are unable to predict the length of the efficacy of laser treatment.

### Comments

Lasers have shown no adverse effects, other than sensation during treatment.

### Photodynamic therapy

Photodynamic therapy (PDT) uses the application of a topical photosensitizing agents and exposure to red or blue light to activate the photosensitizer in order to generate the free radicals to kill the fungi. There are two commercially available photosensitizers that have been tested off-label for use in onychomycosis: 5-aminolevulinic acid and methylaminolevulinate (MAL).

### Toenails (quality of evidence: 2)

No RCTs were found for the treatment of onychomycosis with PDT. One single-assignment open label study investigated MAL-PDT for toenail onychomycosis [117].

### Toenails: effectiveness

After 10 nights of pretreatment with 20% urea ointment, participants applied 16% MAL for 3 h and their nail plates were irradiated with a 570–630 nm light source for a total of three treatments at 2 week intervals [117]. Mycological, clinical, and complete cure rates of 37% at 18 months were found.

### Drawbacks

There is only a single clinical trial and several case studies to support the use of PDT in onychomycosis.

### Iontophoresis

Iontophoresis uses electrical current to increase transungual uptake of terbinafine.

### Toenails (quality of evidence: 2)

A randomized, open, active-comparator study of terbinafine gel with and without iontophoresis was conducted using per-protocol analysis [118].

### Toenails: effectiveness

Participants applied a gel terbinafine patch for 4 weeks and the iontophoresis group received two treatments of 100  $\mu$ A/cm<sup>2</sup> at weeks 2 and 4 [118]. An 84% mycological cure rate (negative microscopy) at 12-week follow-up was obtained.

### Drawbacks

There are no RCTs of iontophoresis with follow-up at time periods greater than 3 months.

## General comments

There have been several pharmacoeconomic analyses of the various oral and topical treatments used in dermatophyte onychomycosis. These studies calculate the cost-effectiveness of each therapy on the basis of the efficacy results of multiple clinical trials. The most cost-effective regimens of oral antifungals for the treatment of onychomycosis are terbinafine (continuous) and itraconazole (pulse) [119,120]. Two studies comparing topical ciclopirox with the two systemic antifungals showed its inferiority to terbinafine and its superiority to itraconazole [121,122]. Combined therapy of the two

antifungals with amorolfine nail lacquer was also superior to the monotherapies [98,123].

In certain nail presentations, the response to therapy may be improved by combining oral antifungal therapy with either an effective topical therapy or mechanical/chemical measures (e.g., mechanical avulsion, debridement, or chemical avulsion). For example, when there is lateral onychomycosis, a dermatophytoma, severe onycholysis, a thickened nail, or severe onychomycosis, it may be advantageous to consider a combination approach [97,124–128].

### Key points

- The main oral antifungal agents used to treat onychomycosis are terbinafine, itraconazole, and fluconazole. Griseofulvin and ketoconazole are the traditional antifungal agents whose utility for onychomycosis has decreased substantially since the availability of the new oral antifungal agents. In addition, the use of ketoconazole for onychomycosis when long-duration therapy is required has diminished markedly, given the potential for hepatotoxicity.
- The preferred regimens with the new oral antifungal agents are terbinafine (continuous), itraconazole (pulse), and fluconazole (once weekly). The duration of therapy with these agents for fingernail onychomycosis is typically as follows: terbinafine continuous (6 weeks), itraconazole pulse (two pulses), and fluconazole once weekly (6–9 months). The corresponding duration of therapy with these antifungal agents for toenail onychomycosis is 12 or 16 weeks, three or four pulses, and 9–15 months, respectively.
- RCTs have demonstrated that griseofulvin, terbinafine (continuous), itraconazole (pulse and continuous), and fluconazole are effective and safe for the treatment of dermatophyte fingernail and toenail onychomycosis.
- Few RCTs have been conducted for the topical nail lacquer formulations. Although the safety of monotherapy with nail lacquers appears to be good, more rigorous clinical trials need to be done to establish with certainty the efficacy of nail lacquers. Current practice would indicate that the addition of a nail lacquer to an established oral regimen may be a consideration in clinical settings.
- Device-based therapies for onychomycosis have shown promising preliminary results, and several laser systems have been FDA-cleared for this indication based on their substantial equivalence to previously approved laser systems [129]. However, more RCTs with participants with mycologically proved onychomycosis that assess the mycological, clinical, and complete cure rates are needed to be able to compare them with the oral and topical antifungals.
- There are several factors that need to be considered when deciding which agent to prescribe for onychomycosis; these include efficacy, the causative organism, regimen preference (e.g., continuous versus pulse versus once weekly, expected duration of therapy), the safety of the antifungal agent, the patient's medical status, the potential for drug interactions, relapse rates, and the cost of therapy.
- None of the newer oral antifungal agents has been approved for the treatment of onychomycosis in children, in whom the disease occurs much less frequently.

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# Tinea capitis

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## Background

### Definition

Tinea capitis (scalp ringworm) is an infection of the scalp skin and hair caused by fungi (dermatophytes) mainly of the genera *Trichophyton* and *Microsporum* [1]. The clinical hallmark is single or multiple patches of hair loss, sometimes with a “black dot” pattern (Figure 44.1), which may be accompanied by signs of inflammation such as scaling, pustules and itching.

### Incidence/prevalence

Tinea capitis is uncommon in adults and is seen predominantly in prepubertal children [2]. It has affected mainly disadvantaged communities in both developing and industrialized nations. Travel and migration have led to changes in the epidemiology of the species of dermatophyte causing tinea capitis.

### Etiology

Tinea capitis is contagious. It can be acquired through contact with people, animals, or objects carrying the fungus [3]. The presence of fungi within the scalp may not be sufficient to result in tinea capitis (carrier state). Approximately eight dermatophyte species are characteristically associated with tinea capitis. Infections due to *Trichophyton tonsurans* predominate from Central America to the USA and in parts of western Europe. *Microsporum canis* infections are mainly seen in South America, Southern and Eastern Europe, Africa, and the Middle East. *Trichophyton mentagrophytes* and *M. canis* are majority pathogenic fungi in China, which mainly come from animals in rural areas or pets in urban areas.

### Prognosis

Tinea capitis is not life threatening in people with normal immunity. Untreated cases cause persistent symptoms, and in some types of tinea capitis (mainly the inflammatory type or kerion) may lead to scarring alopecia (Figure 44.2).

### Diagnostic tests

The clinical diagnosis should be confirmed by mycological examination [4]. The diagnosis of tinea capitis is best undertaken with more than one sampling method: scraping of scalp, scalp massage

brush, toothbrush, or a moistened cotton gauze swab. Microscopy provides the most rapid means of diagnosis and allows treatment to commence, but is not always positive. Culture allows accurate identification of the organism involved and may be positive even when microscopy is negative, but may take up to 4 weeks. Wood's light or filtered ultraviolet light can be used to identify infections that fluoresce under this type of light, such as *M. canis* and *Microsporum audouinii*, but not *T. tonsurans*.

### Aims of treatment

The first aim of treatment is to achieve complete clinical and mycological cure as quickly as possible, with no or minimal adverse effects [5]. Effective short-course therapy is especially desirable in children, because prolonged therapy increases the risk of adverse effects as well as noncompliance. Another goal is prevention of spread to other children from objects, infected animals or children, and from asymptomatic carriers.

### Relevant outcomes

Outcomes are based on resolution of the clinical signs (redness, scaling, edema, and hair loss) and symptoms (itch and pain), and negative mycological data, including microscopy and culture. Complete cure (clinical and mycological cure), cure (clinical or mycological cure), improvement (clinical), and failure (ineffective therapy or worsening) are the most widely used outcomes.

### Methods of search

The methodology of search used for this chapter is an adaptation of the search strategy used in a Cochrane systematic review [6] covering the Cochrane Central Register of Controlled Trials (The Cochrane Library), Medline, and LILACS. Any key randomized clinical trial (RCT) has been included if published by July 2012.

## Systemic antifungal therapy for tinea capitis in children

Griseofulvin has been the most widely used and prescribed treatment for tinea capitis and has served as a standard for the evaluation of any newer agent to be considered for this infection. New drugs used against other fungal infections in adults, such as



Figure 44.1 Tinea capitis.



Figure 44.2 Inflammatory tinea capitis.

ketoconazole, itraconazole, terbinafine, and fluconazole, are being considered more frequently for the treatment of tinea capitis.

## Questions

### In children with tinea capitis, which oral antifungal drug leads to high rates of cure with the fewest adverse events?

#### Griseofulvin

There is moderate RCT evidence that griseofulvin at dosages of 125–500 mg/day (depending on the patient's weight) for 6–8 weeks is effective and safe for the treatment of tinea capitis caused by *T. tonsurans*, *Trichophyton violaceum*, and *M. canis*.

#### Efficacy

Thirteen RCTs compared griseofulvin with other oral antifungals in tinea capitis.

**Different doses** A single-blinded RCT [7] in South Africa (*T. violaceum*) compared two doses of griseofulvin (50 mg/kg) administered 4 weeks apart; weekly doses of griseofulvin (50 mg/kg) for 6 weeks; and daily 6-week course of griseofulvin (10 mg/kg). The mycological cure rates for the groups were 84% (15 of 18), 79% (15 of 19), and 91% (20 of 22), respectively. At 6 months, the mycological cure rates for the three groups remained similar: 92% (11 of 12), 82% (9 of 11), and 95% (16 of 17), respectively. Although the total clinical score fell faster in the daily for 6 weeks group, there was no statistically significant difference in the scores at either 6 weeks or 6 months.

**Versus ketoconazole** Four RCTs were identified. In two RCTs [8,9] (*T. tonsurans*) griseofulvin at dosages of 10–20 mg/kg per day and 250–500 mg/day was compared with ketoconazole 3.3–6.6 mg/kg per day and 200 mg/day for 12 weeks and 6 weeks, respectively. Cure rates in the griseofulvin groups at the end of treatment were 96% and 57.1%, in each study, respectively. A small RCT [10] including 47 children compared griseofulvin 350 mg/day for 6 weeks with ketoconazole 100 mg/day for 6 weeks in inflammatory tinea capitis (*T. mentagrophytes* and *M. canis*). At the end of treatment, 80% and 100% of the children, respectively, had improved clinically, but no mycological data were reported. An RCT with unknown blinding [11] including 63 children (*Trichophyton* spp.

predominated) compared griseofulvin 15 mg/kg per day with ketoconazole 5 mg/kg per day, each given as a single daily dose, and treatment stopped when there was complete cure or after 6 months. After 8 weeks' therapy, 92% of the patients given griseofulvin had complete cure, in comparison with only 59% of the ketoconazole-treated patients. After 12 weeks, 96% of the griseofulvin patients were mycologically cured, in comparison with 74% of the ketoconazole-treated group. Hair sample cultures took significantly longer to become sterile in ketoconazole-treated patients (median 8 weeks) than in griseofulvin-treated patients (4 weeks). However, as other oral azolic antifungals such as itraconazole and fluconazole are available, and as ketoconazole is associated with rare but important hepatic and endocrine adverse events (none of these were noted in the pediatric studies described), ketoconazole has not been considered further as a treatment of choice in children with tinea capitis.

**Versus itraconazole** One RCT [12] in 34 children (*M. canis*) comparing 6 weeks of ultramicrosized griseofulvin 500 mg/day and itraconazole 100 mg/day showed a complete cure rate of 88% for the two drugs after 14 weeks' follow-up.

**Versus fluconazole** Three RCTs comparing fluconazole and griseofulvin were found. The first RCT [13] assessed 100 children (*T. tonsurans* and *T. violaceum*). The children were treated either with fluconazole 6 mg/kg per day for 2–3 weeks or with microsized griseofulvin 20 mg/kg per day for 6 weeks, and the complete cure rates were 82% and 92%, respectively. The second RCT [14] compared 40 children (*T. violaceum*, *Trichophyton verrucosum*, and *M. canis*) treated with 5 mg/kg per day of fluconazole or 15 mg/kg per day griseofulvin for 4 weeks and 6 weeks, respectively. Complete cure was reported for 79% and 76%, respectively. The third study, a three-arm RCT [15] of 880 patients (*T. tonsurans*) compared fluconazole 6 mg/kg per day for 3 weeks followed by 3 weeks of placebo, fluconazole 6 mg/kg per day for 6 weeks, and griseofulvin 11 mg/kg per day for 6 weeks. The complete cure rates were 44.5%, 49.6%, and 52.2%, respectively.

**Versus terbinafine** Eight RCTs were identified. A double-blind RCT [16] compared 140 children from Pakistan (*T. violaceum*). They were treated with either terbinafine (by weight) for 4 weeks or with griseofulvin 6–12 mg/kg per day for 8 weeks. After 12 weeks, 93%

of the terbinafine group was completely cured, in comparison with 80% of the griseofulvin group. A double-blind RCT [17] evaluated 50 children from Peru (*T. tonsurans*). Half were treated with terbinafine according to weight for 4 weeks; the other half received micro-sized griseofulvin according to weight for 8 weeks. After 8 weeks of treatment, complete cure was noted in 76% of the griseofulvin group and in 72% of terbinafine group, but 4 weeks later the complete cure rate increased to 76% in the terbinafine group, while in the griseofulvin group it had fallen to 44%. A large RCT [18] (*T. tonsurans*) compared 8 weeks of griseofulvin suspension 10 mg/kg per day with 4 weeks of terbinafine. The complete cure rates at week 24 were 64% and 67%, respectively. However, there was a trend to better responses in a few cases with *Microsporum* spp. infections with 8 weeks of griseofulvin than with 4 weeks of terbinafine. In another RCT [19] the complete cure rate at the final follow-up visit (week 12) was 74% in the group treated for 8 weeks with ultramicrosized griseofulvin, in comparison with 78% in the group treated with terbinafine for 4 weeks, with no significant differences between *M. canis* and *Trichophyton* spp. infections. Another trial [13] compared 50 patients in each treatment group (*T. tonsurans* and *T. violaceum*). In this trial, terbinafine for 2–3 weeks was compared with micro-sized griseofulvin 20 mg/kg for 6 weeks. The complete cure rate was 94% for the terbinafine group and 92% for the griseofulvin-treated group. Only one RCT [20] assessed medium-term to long-term treatment regimens comparing terbinafine with griseofulvin (*M. canis*). The patients were treated with terbinafine for 6, 8, 10, or 12 weeks, followed by placebo to complete a 12-week treatment phase in a double-blinded regimen, or griseofulvin for 12 weeks using an unblinded regimen. Medium-term treatment (6 or 8 weeks) resulted in a trend towards an increase in the complete cure rate in the griseofulvin group in comparison with the terbinafine group at 4 weeks after the end of treatment. However, long-term treatment (10 or 12 weeks) resulted in the complete cure rates being significantly higher in the griseofulvin group in comparison with the terbinafine group at 4 weeks after the end of treatment. An RCT [21] compared (*Trichophyton* infections) 4 weeks of griseofulvin, 2 weeks of terbinafine, and 4 weeks of terbinafine. The clinical cure rates were 84.2%, 85.2%, and 78.3%, respectively, at week 8 and 100% after 1 year for all agents. Two identical RCTs in children [22] compared once-daily treatment with terbinafine (5–8 mg/kg) or griseofulvin (10–20 mg/kg) for a period of 6 weeks. Complete cure rates were statistically significantly greater for terbinafine compared with griseofulvin in trial 1 (46.23% vs 34.01%) but not in trial 2 (43.99% vs 43.46%). Subgroup analyses revealed that terbinafine was significantly better than griseofulvin for all cure rates (mycologic, clinical, and complete) among patients with *T. tonsurans*. For *M. canis*, mycological and clinical cure rates were significantly better with griseofulvin than with terbinafine.

### Drawbacks

The most common adverse events in the griseofulvin group were nausea, abdominal discomfort and vomiting, headaches, minor disturbances in taste, and pyrexia; almost all were mild or moderate in severity. None of the events was rated as severe. In other studies, no adverse effects or no significant adverse effects were reported.

### Comments

All included studies show that griseofulvin is effective for tinea capitis. The high patient drop-out rate in most of the studies may have masked the improvement in the griseofulvin groups, as those who achieve cure may have less incentive to attend follow-up visits.

It will also have reduced the power to detect a difference between the groups, indicating that griseofulvin may be even more effective. The duration of follow-up varies from study to study (4 weeks–1 year), and only RCTs with long-term follow-up can show the relapse rates, which are very important in determining therapeutic efficacy.

### Implications for practice

There is good evidence to support the use of griseofulvin to treat tinea capitis caused by *T. tonsurans*, *M. canis*, *T. mentagrophytes*, and *T. violaceum*. Overall, griseofulvin is considered to be safe in children. On the basis of the RCTs described, the recommended dosage regimen for children is continuous therapy with tablets or suspension, adjusted according to the patient's weight (10–20 kg: 125 mg/day; 20–40 kg: 250 mg/day; >40 kg: 500 mg/day) for 6–8 weeks, including micro-sized and ultramicrosized preparations. Other advantages of griseofulvin are that it is inexpensive and that the suspension allows accurate dosage in children. Griseofulvin is licensed for the treatment of tinea capitis in most countries.

### Terbinafine

Moderate RCT evidence indicates that terbinafine at dosages of 62.5–250 mg/day (depending on body weight) for 2 weeks in *T. violaceum* infections and for 4 weeks in *T. tonsurans* infections is effective and safe for the treatment of tinea capitis. A few RCTs (limited evidence) suggest that longer therapeutic regimens of 6 weeks may be necessary to treat *Microsporum* spp. infections.

### Efficacy

**Different terbinafine regimens compared** Four RCTs were found. One RCT [23] (*T. violaceum*) compared 1, 2, and 4 weeks of terbinafine therapy, 62.5–250 mg depending on weight. The cure rates were 49% after 1 week of therapy, 61% after 2 weeks, and 67% after 4 weeks. A second RCT [24] compared 1, 2, and 4 weeks of terbinafine, 62.5–250 mg depending on weight, in 79 children and three adults (*T. tonsurans* and *Microsporum ferrugineum*). At week 12, the complete cure rates were 44% in the 1-week therapy group, 57% in the 2-week therapy group, and 78% in the 4-week group. An RCT [25] published in two additional abstracts [26,27] compared 1 week and 2 weeks of terbinafine, 62.5–250 mg depending on weight. At week 12 of follow-up, in *Trichophyton* spp. infections the complete cure rate was 44.4% with 1 week of therapy and 64% with 2 weeks, but acceptable cure rates in *M. canis* infection were achieved only after an additional 4 weeks of treatment. An RCT [28] including 107 children (*M. canis*) compared 1, 2, and 4 weeks of terbinafine, 125–250 mg/day depending on weight. At week 12, the mycological cure rate was 46% with only 1 week of therapy, 53% with 2 weeks, and 69% with 4 weeks. In another RCT [29] that compared different regimens of terbinafine at dosages of 3–6 mg/kg per day for 1, 2, or 4 weeks, the complete cure rates were 38%, 46%, and 48% for the 1-week, 2-week, and 4-week arms, respectively. Another RCT [30] assessed the efficacy of the standard dose of terbinafine in comparison with double doses of terbinafine, both given in a pulsed protocol (1 week on, 3 weeks off) in the treatment of *Microsporum* spp. tinea capitis. There were no statistical differences in the cure rates between standard and double-dose pulsed therapy at week 20; the standard-dose group achieved a complete cure rate of 60.8%, while the double-pulse group reached 68.4%.

Seven RCTs compared terbinafine with other oral antifungals in tinea capitis.



**Versus griseofulvin** Eight RCTs were identified and they have been commented in the previous section on griseofulvin.

**Versus itraconazole** One RCT [31] compared (*T. violaceum*) 2-week courses of terbinafine 62.5–250 mg and itraconazole 50–200 mg (both depending on weight). Twelve weeks after the start of treatment, 78% and 86% of the patients were completely cured in the terbinafine and itraconazole groups, respectively. Another RCT [13] compared (*Trichophyton* species) itraconazole and terbinafine in a 2–3-week course of therapy; the complete cure rates at 12 weeks were 94% for the terbinafine group and 82% for the itraconazole group.

**Versus fluconazole** The same RCT [13] analyzed the efficacy of fluconazole for 2–3 weeks in comparison with terbinafine, dosed according to weight for 2–3 weeks. The complete cure rates were 82% in the fluconazole arm and 94% in the terbinafine arm, similar to the results for griseofulvin.

### Drawbacks

Tolerability was generally reported as good, with no or few mild to moderate adverse events of uncertain relationship or unrelated to the drug: headache, fatigue including somnolence, nausea, dyspepsia and abdominal pain, mild constipation, pruritus, urticaria, labial edema, moderate loss of appetite, mild diarrhea, mild and moderate partial loss of taste (recovered within 8 weeks), coughing and fever, raised hepatic enzymes, raised triglycerides, eosinophilia, leukocytosis, and neutropenia.

### Comments

An RCT [32] of a group of New Zealand patients (*M. canis*) was excluded because it did not provide separate clinical and mycological data for each study group. The manufacturer of terbinafine has been involved in most of the RCTs. The definition of cure varies from study to study; some investigators follow microbiological findings, while others place greater emphasis on clinical response. High drop-out rates in some studies may artificially decrease the response rate, as those who are cured may be lost to follow-up.

### Implications for practice

There is good evidence to support the use of terbinafine for treating *T. tonsurans* tinea capitis in children, and fair evidence to support its use in *M. canis* tinea capitis. Terbinafine has an advantage over griseofulvin in that it produces good results in a shorter time, making patient compliance less of a problem. An important disadvantage is that it is available only in tablet form; there is no suspension. It is also much more expensive than griseofulvin. According to the RCTs, the recommended regimen in children with tinea capitis is continuous therapy once daily for 4 weeks, with dosage according to body weight: 62.5 mg/day for children weighing 10–20 kg; 125 mg/day for those weighing 20–40 kg; 250 mg/day for those weighing over 40 kg. Analysis of the respective studies showed that treatment duration of 4 weeks is clearly better than 1 week and 2 weeks. *M. canis* infections may require treatment for 6–8 weeks (griseofulvin is likely to be superior to terbinafine for the cases of infections by *Microsporum* species). Terbinafine is not licensed for this indication in children in some countries.

### Itraconazole

Limited RCT evidence shows that oral itraconazole at dosages depending on the patient's weight (<20 kg: 50 mg/day; >20 kg: 100 mg/day) for 2–6 weeks is effective and safe for tinea capitis

caused by *T. violaceum* (2 weeks of treatment) and *M. canis* (6 weeks of treatment). Only observational data suggest that itraconazole may be effective against *T. tonsurans* infections.

### Efficacy

Three RCTs compared itraconazole with other oral antifungals.

**Versus griseofulvin** See section on griseofulvin.

**Versus terbinafine** See section on terbinafine.

**Versus fluconazole** In an RCT [13], itraconazole in patients with *Trichophyton* infections, at a dosage of 5 mg/kg per day daily for 2–3 weeks, was compared with fluconazole; the complete cure rates were 82% in both groups.

### Drawbacks

Transient gastrointestinal side effects are the most frequently reported, and rarely a reversible increase in serum aminotransferase. Other less frequent reported side effects are urticaria, headache, and “tired legs.”

### Comments

The methods of randomization and blinding were not clearly described in some RCTs. Only one of the RCTs [12] was funded by the manufacturer of itraconazole. More, but less reliable, information is available from uncontrolled studies, but additional RCTs comparing itraconazole with other antifungals are clearly needed.

### Implications for practice

There is fair evidence to support the use of itraconazole for the treatment of tinea capitis caused by *M. canis*, *T. violaceum*, and *T. tonsurans* in children. On the basis of the available evidence, the recommended dosage for itraconazole for tinea capitis in children is 100 mg/day or dose adjusted to body weight, for 6 weeks in *M. canis* and for 2 weeks in *T. violaceum* infections. Uncontrolled studies suggest that shorter or pulse regimens may also be useful.

### Fluconazole

Limited evidence suggests that fluconazole continuously at 6–8 mg/kg per day for 3 weeks or intermittently at 6–8 mg/kg per week for 4–8 weeks is effective and safe for treating *T. tonsurans* and *M. canis* tinea capitis in children.

### Efficacy

**Different fluconazole regimens compared** A small RCT [33] compared various dosages of fluconazole (1.5, 3.0, and 6 mg/kg per day) for 20 days in the treatment of *T. tonsurans* tinea capitis. Complete cure rates were 25% in the 1.5 mg group, 60% in the 3 mg group, and 89% in the 6 mg group.

Three RCTs compared fluconazole with other systemic antifungals for tinea capitis.

**Versus griseofulvin** See section on griseofulvin.

**Versus terbinafine** See section on terbinafine.

**Versus itraconazole** See section on itraconazole.

### Drawbacks

Only mild, reversible gastrointestinal complaints and asymptomatic and reversible elevated liver function tests were noted in an RCT. No adverse effects were reported in some trials.

### Comments

Studies are needed in order to compare fluconazole with other antifungals and to determine the proper dosing and duration of therapy.

### Implications for practice

There is some evidence to recommend a dosage regimen with fluconazole for tinea capitis in children. Observational studies suggest that continuous 6 mg/kg per day for 3 weeks or intermittent 6–8 mg/kg per week for 4–8 weeks may be effective. Fluconazole is not licensed for this indication in children in some countries.

### What are the effects of topical treatment of tinea capitis in adults and children?

Adjunctive topical therapy has been used together with oral antifungal treatment to eradicate the fungi from the infected site, decrease spread to other people, and speed the cure. Various topical agents are available for adjunctive therapy.

### Shampoos

There is moderate RCT evidence that the addition of biweekly shampooing with selenium sulfide substantially reduces the period of active shedding. However, some evidence indicates that topical treatment is not useful for tinea capitis.

### Efficacy

An RCT [34] reported that 75% of griseofulvin-treated patients with uncomplicated *T. tonsurans* tinea capitis had sterile hair sample cultures 4 weeks after initiation of griseofulvin. By contrast, 94% of patients who received griseofulvin together with biweekly selenium sulfide shampoos had sterile hair cultures at 4 weeks. Another RCT [35] of 54 patients receiving griseofulvin 15 mg/kg per day for *T. tonsurans* tinea capitis compared selenium sulfide 2.5% lotion or 1% shampoo with a bland, unmedicated shampoo. Patients were observed every 2 weeks until they were clinically and mycologically cured. The selenium sulfide products were statistically superior to the unmedicated shampoo with regard to the time required to eliminate shedding and viable fungi. However, no difference was noted between the two selenium products. One RCT [36] compared selenium sulfide shampoo 1% and ciclopirox shampoo 1% twice a week as adjuncts to an 8-week course of ultramicronized griseofulvin dosed at 10–12 mg/kg per day. Selenium sulfide shampoo 1% and ciclopirox shampoo 1% were equally effective as adjunctive treatments for tinea capitis in children in our study. Overall, 90.9% of treated children demonstrated mycological cure.

### Soap

An RCT [37] assessed the clinical efficacy of the antimicrobial agent triclosan in bar soap in comparison with regular soap against selected superficial dermatomycoses in Tanzanian schoolchildren. There was no significant difference between the active and placebo groups during follow-up after 2 months for any of the four forms of dermatomycoses.

### Cream/ointment

One RCT [38] was conducted in a region of Africa in which griseofulvin is not generally available. It compared 6 weeks of miconazole cream with 6 weeks of Whitfield's ointment (6% benzoic acid plus 3% salicylic acid) in *T. violaceum* and *M. audouinii* tinea capitis and found no significant cure rates.

### Drawbacks

No adverse events were reported.

### Comments

RCTs of adjunctive therapy were described as randomized, but did not adequately describe the method and were not blinded.

### Implications for practice

There is some evidence to support the use of adjunctive topical therapy for tinea capitis with antifungal shampoos (for example, 1% selenium sulfide shampoo) to reduce the time of cure and to decrease the spread of infectious fungi to other persons. There is also some evidence not supporting the exclusive use of topical agents to treat tinea capitis.

### In children with inflammatory tinea capitis (kerion), does an oral antifungal plus a corticosteroid lead to faster cure and complete hair regrowth than an oral antifungal alone?

#### Corticosteroids

Moderate RCT evidence indicates that the use of oral or intralesional corticosteroids as adjunctive therapy with griseofulvin for inflammatory tinea capitis (kerion) does not lead to additional or faster improvement.

### Efficacy

Three RCTs showed no evidence that the use of intralesional [39] or oral [40,41] corticosteroids as adjunctive therapy with oral griseofulvin in inflammatory tinea capitis (kerion) results in additional or faster improvement of kerion. One RCT [39] of 30 children (*T. tonsurans*) showed that intralesional injection of corticosteroid combined with oral griseofulvin is no better than griseofulvin alone for treatment of kerion, and found no significant differences in the time to negative culture, time of onset of new hair growth, complete regrowth of hair, or time to scalp clearing. In this study, all patients were instructed to shampoo their hair with 1% selenium sulfide twice weekly for 3 weeks. Two small RCTs [40,41] using oral corticosteroids showed no additional benefit in terms of improvement, reduction in the severity of clinical signs, or pathogen eradication.

### Drawbacks

No adverse events were noted. In particular, none of the patients had post-therapy alopecia, permanent scarring, or biochemical evidence of hepatic dysfunction.

### Comments

Whether larger doses of steroid might be effective remains unknown. In an RCT, scaling and pruritus were eliminated more quickly in the group that used oral erythromycin and oral prednisone in addition to griseofulvin, but the authors considered that this may have been due to the smaller volume of the kerions in this group rather than the effects of therapy, so that the patients became symptom free sooner.

### Implications for practice

The addition of corticosteroids to oral antifungals is unlikely to be useful. There is some limited evidence questioning the use of oral or intralesional corticosteroids as adjunctive therapy for inflammatory tinea capitis (kerion).

## What strategies are best for reducing spread and reinfection in tinea capitis in adults and children?

Carrier state is found in individuals with no signs or symptoms of tinea capitis, but from whom positive cultures from the scalp can be isolated. Strategies for management of the carrier state include preventive treatments such as fungicidal shampoos, decontamination of objects that come into contact with the scalp, education programs for children to avoid sharing of objects that can spread tinea capitis to others (such as caps, combs, and toys), and shaving of hair. There is no RCT evidence regarding the optimal management of symptom-free carriers. No RCTs were found concerning the impact of strategies for management of the asymptomatic carrier state.

## Implications for practice

The effectiveness is unknown. Although it is agreed that decontamination of objects that come into contact with the scalp, education programs for children, and avoidance of sharing of objects can reduce the spread of fungal infections, there is no good evidence to support such decontamination procedures. No evidence supports the regular use of antifungal shampoos in controlling the carrier state of populations at risk. Povidone iodine shampoo may be the most suitable for prophylaxis [42].

### Key points

#### Systemic antifungal therapy for tinea capitis in children

- RCT evidence suggests that griseofulvin for 6–8 weeks is effective and safe for tinea capitis.
- The best evidence available also suggests that terbinafine, itraconazole, and fluconazole can cure most patients with tinea capitis with a shorter course of therapy. All these drugs may be preferred because shorter treatment durations may improve treatment adherence, although they may be more expensive. Not all these treatments are available in pediatric formulations, but they have good safety profiles in children. However, there is not enough evidence on the use in children with *Microsporum* infections.
- RCT evidence indicates that terbinafine for 4 weeks is effective and safe for treating *Trichophyton* spp. tinea capitis. Some evidence suggests that longer therapeutic regimens of 6 weeks are necessary to treat *Microsporum* spp. infections.
- Some RCT evidence suggests that oral itraconazole for 2–6 weeks and fluconazole for 3–6 weeks are effective and safe for treating tinea capitis in children.
- Regional as well as dermatophyte species variation may play an important role in the response rate, and may determine what dosage regimens are recommended. Resistance to antifungals could be a major concern in some areas.

#### Adjunctive therapy for tinea capitis in adults and children

- Some RCT evidence suggests that antifungal shampoos can reduce the period of active shedding in patients treated with oral antifungals.
- There is not enough evidence to say whether the addition of oral steroids to antifungal agents improves the resolution of inflammatory tinea capitis.

#### Strategies to reduce spreading and reinfection in tinea capitis

- There is insufficient evidence suggesting that antiseptic shampoos can reduce spread from carriers.
- No RCT evidence exists regarding the optimal management of symptom-free carriers.

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# Deep fungal infections

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## Introduction

Deep fungal infections or mycoses comprise a group of diseases that spread within the subcutaneous tissues (subcutaneous mycoses) or predominantly involve deeper structures, including blood and bone marrow, along with other organs such as the lung and the liver (systemic mycoses). They include a number of different diseases (Table 45.1).

Involvement of the skin in subcutaneous mycoses is usually secondary to direct spread from adjacent sites of infection – as in mycetoma, where sinuses from deep abscesses reach the skin surface. The skin is usually breached during the process of infection, and the organisms are often found in the environment with which the patient has contact.

In the case of the systemic mycoses, skin involvement is less common, but may occur through bloodstream spread, in which the skin lesions are a consequence of dissemination and the formation of active infective foci in the dermis. The lung is usually the portal of entry in infections such as histoplasmosis, known as the endemic respiratory mycoses. Rarely, the skin is the portal of entry in systemic fungal infections, and the clinical course in such cases may be more benign, sometimes responding to minimal therapy. This pattern of infection, in which there is local inoculation followed by local lesions and regional lymphadenopathy, is referred to as the cutaneous chancriform syndrome. By contrast, fully developed and widely disseminated disease spreading via fungemia to affect the skin is often fatal. Infections with certain fungi such as *Talaromyces marneffe* are more likely to result in skin lesions; in the latter infection, over 70% of cases associated with acquired immune deficiency syndrome (AIDS) present with skin lesions. An important subset of systemic mycoses is referred to as the opportunistic mycoses, because there is always an underlying abnormality such as neutropenia or AIDS. Systemic candidosis and aspergillosis belong to this group. Skin involvement is rare and is usually the result of bloodstream spread.

This chapter is largely concerned with the subcutaneous mycoses. The systemic mycoses are, by definition, severe internal infections, and a discussion of their management is beyond the scope of a dermatological work. In addition, there are no clinical studies

directly relevant to the cutaneous manifestations of the systemic diseases, with the exception of a debate about the relevance of direct cutaneous invasion in their pathogenesis.

Subcutaneous infections are rare and are generally confined to developing countries. There are few well-organized clinical studies in these infections, and randomized double-blind controlled trials are exceedingly rare.

The evidence search for this chapter is based on the Cochrane Central Register of Controlled Trials (version 3, 2007) and my own collection of studies and personal contacts in the field. Most drugs used for these infections have been developed to treat other mycotic infections, and their application to deep mycoses is based on individual cases or case clusters. Each of the subcutaneous mycoses is dealt with separately.

## Mycetoma

### Definition

Mycetoma is a subcutaneous infection caused by either fungi (eumycetoma) or actinomycetes (actinomycetoma) (Figure 45.1). The focus of infection is the subcutaneous tissue, including subcutaneous fat. The hallmark of the infection is that the microorganisms involved form into clusters of filaments called grains, which are surrounded by a dense neutrophil response, forming an abscess. These abscesses subsequently discharge onto the skin surface via draining sinuses, but may affect underlying bone, resulting in osteomyelitis. Infective organisms are implanted into the skin, usually following a thorn injury [1].

### Incidence/prevalence

Mycetoma is an uncommon infection (Figure 45.1), and there are no community-based data on its prevalence. Information on the worldwide incidence is based on an old study conducted by postal questionnaire in which interested departments (133) submitted data on numbers of cases occurring between 1940 and 1960. The results were published in 1963 [2], and indicate that certain countries such as Sudan and Mexico had the highest numbers of cases.

Table 45.1 The deep mycoses.

Disease	Pathogens
<i>Subcutaneous mycoses</i>	
Mycetoma	<i>Madurella mycetomatis</i> , <i>M. grisea</i> (fungi) <i>Nocardia</i> spp., <i>Streptomyces somaliensis</i> (actinomycetes) and others
Chromoblastomycosis (chromomycosis)	<i>Fonsecaea pedrosoi</i> , <i>Cladophialophora carrionii</i> , and others
Sporotrichosis	<i>Sporothrix</i> spp.
Lobomycosis	<i>Lacazia loboi</i> (previously called <i>Loboia loboi</i> )
Subcutaneous zygomycosis	<i>Basidiobolus</i> or <i>Conidiobolus</i> spp.
<i>Systemic mycoses</i>	
<i>Endemic respiratory infections</i>	
Histoplasmosis	<i>Histoplasma capsulatum</i> var. <i>capsulatum</i>
African histoplasmosis	<i>H. capsulatum</i> var. <i>duboisii</i>
Blastomycosis	<i>Blastomyces dermatitidis</i>
Coccidioidomycosis	<i>Coccidioides immitis</i>
Paracoccidioidomycosis	<i>Paracoccidioides brasiliensis</i>
Infections due to <i>Penicillium marneffei</i>	<i>Talaromyces marneffei</i>
<i>Opportunistic infections</i>	
Systemic candidosis	<i>Candida albicans</i> , <i>C. tropicalis</i> , <i>C. glabrata</i>
Aspergillosis	<i>Aspergillus fumigatus</i> , <i>A. flavus</i> , <i>A. niger</i>
Cryptococcosis	<i>Cryptococcus neoformans</i>
Mucormycosis (invasive zygomycosis)	Species of <i>Absidia</i> , <i>Rhizopus</i> , and <i>Rhizomucor</i>
Others	Infections due to <i>Fusarium</i> , <i>Trichosporon</i>

However, some countries such as India, in which the disease is endemic, did not participate, so that the data are incomplete.

Etiology and risk factors

Infections follow traumatic implantation of contaminated material from the environment. Because there are no known animal models, the method of infection is unknown. There are also no known risk factors apart from rural occupation. One report suggested that there was a higher incidence of diabetes mellitus in those with the disease, but it did not include appropriate controls, and the observation has not been substantiated elsewhere [3].

Prognosis

There are no studies indicating the prognosis of this infection. Most patients have been found to have some morbidity, usually resulting from limb deformity, but death has been known to occur in cases in which the infection affects the scalp or chest wall.

Treatment aims

The primary aim in the treatment of mycetoma is to eradicate the infection and thereby halt the progression of deformity. This is possible in the case of actinomycetomas, which are bacterial infections;



Figure 45.1 A eumycetoma infection.

however, there is insufficient evidence to support a particular regimen of treatment for eumycetomas, although individual responses have been recorded for ketoconazole, itraconazole and terbinafine, and amphotericin B [4]. Generally, the response rates amongst eumycetoma infections to chemotherapy are low and unpredictable. Increased chances of cure are associated with longer treatment duration, whereas size (above 5 cm diameter ) and the use of combined surgery and medical treatment are indicators of likely treatment failure [5]. In eumycetoma, a secondary objective is to slow the course of the disease, thus delaying the time when amputation becomes necessary. Amputation provides a radical cure.

Outcomes

Outcomes range from recovery to slowing of the disease progress. Mycetoma is rarely fatal, and the main problems even in extensive disease are deformity and disability. In a few cases in which the disease affects areas close to vital structures, such as the chest wall or cranium, the outcome is fatal.

The main approaches to management are therefore chemotherapy, combined in some cases of eumycetoma with surgery. Surgery itself may remove tissue from weight-bearing areas in which the lack of support may result in pain and further disability.

Can mycetoma be treated successfully?

Efficacy

The usual treatments are chemotherapy for actinomycetomas and surgery and/or chemotherapy for eumycetomas. I have been unable to find any systematic reviews of treatment, and there are no controlled clinical trials. Good responses to drugs such as sulfonamides and sulfones, as well as co-trimoxazole, have been reported in the management of actinomycetomas [6], and the addition of amikacin has been evaluated in an open study [7]. Treatment of eumycetoma with chemotherapy produces unpredictable results [4] and recovery is unusual. Radical surgery, including limb amputation, is curative in most cases.

Drawbacks

There are also no studies reporting side effects of therapy in the specific case of mycetoma. The adverse events related to azoles such as ketoconazole and itraconazole are symptomatic hepatitis (rare with itraconazole), toxic epidermal necrolysis, and drug interactions with some common medications such as terfenadine, astemi-

zole, ciclosporin, tacrolimus, digoxin, and statins, interaction with the latter resulting in rhabdomyolysis.

### Comments

Mycetoma is a rare disease caused by more than 10 different micro-organisms distributed throughout much of the developing world. A new generation of clinical trials to provide the foundation for an evidence-based review of treatment remains unlikely and could only be achieved with a coordinated multinational approach.

### Implications for clinical practice

Treatment is likely to continue to be based on anecdotal evidence of the efficacy of different regimens.

#### Key points: mycetoma

- Treatment of actinomycetoma usually depends on two drugs, such as co-trimoxazole plus rifampicin. The latter is given for up to 6 months, while the other medication is continued until clinical recovery.
- Sulfonamides or sulfones can be used instead of co-trimoxazole, and streptomycin instead of rifampicin [4,7].
- Another proposed two-step regimen based on a small case series involves an intensive phase of therapy with penicillin, gentamicin, and co-trimoxazole for 5–7 weeks, followed by maintenance therapy with amoxicillin and co-trimoxazole [8].
- A successful outcome of treatment is less likely for eumycetomas. Therapy is therefore based on the premise of control of the infection by suppression of the disease, using fluconazole [9], itraconazole [10,11] or terbinafine [12], voriconazole [13] plus amphotericin B [4]. Patients are followed over years.
- Where necessary, surgery is used to supplement the medical approach for slowing eumycetomas. Indications for amputation are advancing disease threatening the whole limb (for example, involvement of the femur) and severe pain.
- Arterial perfusion with amphotericin B has also been tried for eumycetoma, with variable success rates [14].

## Sporotrichosis

### Definition

Sporotrichosis is a subcutaneous and systemic infection caused by *Sporothrix* species, such as *S. schenckii*, a dimorphic fungal pathogen found in leaf and plant debris. The subcutaneous variety described here presents with solitary or lymphangitic nodules or ulcers on exposed cutaneous sites.

### Incidence and prevalence

This is an uncommon infection and there are few data on its prevalence. A problem in estimating the exposure is that the frequency of subclinical infection is unknown. Using the crude antigen sporotrichin, it appears that many of the local unaffected population in endemic areas have positive reactions to the skin test (for example, 22%) [15], but it is not clear if this is the result of exposure to *Sporothrix* spp. or to cross-reactive fungal species.

By plotting the spread of cases, it appears that sporotrichosis is mainly seen in the tropics and subtropics and in parts of the USA. Before the 1940s, it was regularly seen in Europe, where it is now uncommon.

It is clear that cutaneous sporotrichosis may occur in the form of isolated cases or in case clusters associated with exposure to a common source of infection, such as straw used in packing [16]. A major and continued outbreak was associated with contaminated pit props used in mines in South Africa. In addition, it appears that there are areas termed hyperendemic in parts of the world – for example, Guatemala, Mexico, Brazil, and Peru. In Brazil, a major risk factor for infection appears to be spread from infected cats [17].

### Etiology and risk factors

Infections follow traumatic implantation of infected material from the environment, although it is not clear whether this is always followed by clinical disease. Risk factors include occupation – for example, miners, flower workers, those using plant material for packing, and armadillo hunters have all been described as being at risk from exposure.

### Prognosis

There are no studies to show whether there is spontaneous resolution, but this seems possible. There is clearly a wider spread of cutaneous lesions in patients with AIDS, and there is a risk of internal dissemination from skin lesions in such cases. Rare cases of systemic sporotrichosis usually appear to have arisen independently of skin injury and are thought to have followed inhalation and subsequent dissemination from the lung.

### Treatment aims

The aim of treatment is cure of the disease. Generally, full recovery is achievable.

### What is the best treatment for sporotrichosis?

#### Efficacy

The classic treatment of sporotrichosis is a saturated solution of potassium iodide. It is started at a dosage of 1 mL three times daily, and the dose is increased dropwise until 4–6 mL is being administered three times daily [18,19]. The solution is often associated with side effects such as nausea, vomiting, and swelling of the salivary glands. However, terbinafine, itraconazole, and fluconazole have recently been used with some success in this infection [19–22].

Saturated potassium iodide is still widely used because it is cheap. One unblinded randomized comparative study of 57 people with culture-confirmed sporotrichosis showed that there was no advantage in splitting the dose of potassium iodide into three and that a single daily dose was as effective and no more toxic, with cure rates of around 89% in both groups after 45 days of follow-up [23]. The alternative therapies are itraconazole 100–600 mg daily and terbinafine 250 mg daily. Itraconazole given for up to 36 months is recommended in a guideline for cutaneous sporotrichosis by the American Infectious Disease Society [24]. The efficacy of itraconazole is mainly supported by open studies [20,21], and there are fewer studies of terbinafine [12]. A study comparing continuous (100 mg daily) versus pulsed (200 mg twice daily for 1 week in every 4 weeks) itraconazole showed no significant difference between the two treatment regimens [25]. Patients with lymphocutaneous sporotrichosis respond slower to itraconazole than those with the fixed pattern of infection [21]. However, a recent trial comparing terbinafine in two dose forms, 1000 mg versus 500 mg daily, has demonstrated better results (87% vs 52% clinical cure) and fewer relapses up to 24 weeks after the end of treatment [26]. A bidirectional cohort study in Brazil found that 250 mg terbinafine daily was equally effective compared with 100 mg itraconazole, although in

a few individual patients the dose of both drugs had to be doubled [27]. One study of fluconazole 200–800 mg daily [22] produced a cure in 10 of 14 patients (71%) with lymphocutaneous sporotrichosis.

Other proposed methods of treatment include liquid nitrogen as cryotherapy [28]. I have been unable to find any systematic reviews of treatment.

### Drawbacks

There are few studies reporting side effects of therapy specific for sporotrichosis, and readers are referred to references to itraconazole and terbinafine. Potassium iodide causes other specific side effects, such as sickness, vomiting, hypersalivation, and salivary gland swelling. These side effects are common (affecting around half of the trial participants in the one study described above [23]) and usually mild.

### Comments

There are opportunities for controlled studies of therapy in sporotrichosis, even though the disease is uncommon in many areas.

### Implications for clinical practice

Given the absence of randomized controlled studies that evaluate different treatment approaches for sporotrichosis, the current recommendations are based mainly on experience and open studies.

#### Key points: sporotrichosis

- The main treatments in use are saturated potassium iodide solution and itraconazole.
- The disadvantage of potassium iodide is the high frequency of side effects, but the preparation is cheap.
- Fluconazole and terbinafine are alternatives, both of which show efficacy.
- Itraconazole appears to be effective, but is used for similar long treatment periods to those used with potassium iodide. More comparative studies with terbinafine and fluconazole are needed.

## Chromoblastomycosis

### Definition

Chromoblastomycosis is a subcutaneous infection caused by a number of different fungi, such as *Cladophialophora carrionii* and *Fonsecaea pedrosoi*; a less common cause is *Phialophora dermatitidis*. The infection starts in the subcutaneous tissue or dermis, and this is followed by progressive enlargement of cutaneous plaques, which are usually either verrucose or plaque-like, with central scarring. The organisms can be found in skin scrapings or biopsies as small pigmented cells, often divided by a cross-wall.

### Incidence and prevalence

This is an uncommon infection and there are no data on its prevalence. The disease is therefore known by clinical anecdote and reported cases. The endemic zone includes the tropics, particularly the humid zones; countries such as Costa Rica, Brazil, and Madagascar probably have the largest number of cases [29].

### Etiology and risk factors

Infection follows traumatic implantation of material from the environment. Fungi such as *Fonsecaea* species can be isolated from

leaves and plant material. Although agricultural workers appear to be most at risk, there are no multicenter studies evaluating this issue [29].

### Prognosis

There are no studies indicating the prognosis of this infection. However, a small proportion of patients (5%) may progress to squamous carcinoma of the skin in the affected area.

### Treatment aims

The primary aim of treatment is complete recovery [29]. This is not always achievable in advanced disease. A secondary aim is prevention of complications such as squamous cell carcinoma.

### Outcomes

As stated above, full recovery is not always achievable, although in early cases full recovery can be expected.

### What is the best treatment for chromoblastomycosis?

#### Efficacy

The treatment of chromoblastomycosis is complex. I have not found any controlled clinical studies of therapy. It is not clear, however, whether a single drug can cure extensive disease. Most of the treatment failures appear to occur when the infection covers a wide area.

The main treatments currently in use are itraconazole and terbinafine. Itraconazole has been used in doses of 100–400 mg daily with good results, particularly in early cases [30,31]. Terbinafine has been used in doses of 250 mg daily, also with good responses [32,33]. There is less experience with fluconazole, although it has been cited as an effective therapy [34]. There is no clear evidence that there are different responses to the two agents. In unresponsive cases, alternatives include combination therapy with amphotericin B and flucytosine [35], or itraconazole and flucytosine [36], or itraconazole and fluconazole [31]. Physical methods such as heat therapy and cryotherapy have also been used. Heat therapy involves application of heat-retaining materials to the lesions, repeated daily or less frequently over a number of weeks [36,37]. Prolonged treatment with repeated episodes of cryotherapy has been shown to lead to the resolution of lesions without relapse during a 3-year follow-up period in 41% of patients [38]. Itraconazole has also been used in a pulsed format [39] and in combination with physical methods. One comparative trial of 12 patients with histologically confirmed chromoblastomycosis evaluated the benefit of cryotherapy in addition to itraconazole [40]. The authors suggested that itraconazole can be used initially to reduce the size of lesions, with cryotherapy being given to the residual lesion. Topically applied ajoene under occlusion has been compared with topical fluorouracil (5-FU) in the management of chromoblastomycosis due to *C. carrionii*. Both were reported to be effective, with over 74% cure rates. There was a higher risk of post treatment scarring in the patients receiving the 5-FU [41].

### Drawbacks

The potential risks of treatment with terbinafine and itraconazole are discussed elsewhere in this volume. Flucytosine is an oral/intravenous drug. Potential side effects include nausea, diarrhea, and headache, and dose-dependent bone-marrow suppression. The latter occurs when plasma flucytosine levels exceed 100 mg/mL. The dose of flucytosine should be reduced in patients with renal impairment (there is a useful guide in the packet insert), and it is



difficult to obtain in many parts of the world where this disease is endemic. Full blood and platelet counts should be followed during therapy; electrolyte and urea levels are also indicative of impending renal impairment. It is possible to monitor serum levels of flucytosine, reducing the dose if necessary. The optimum level is 40–60 mg/mL.

### Comments and implications for clinical practice

The best approach to treatment in most cases is to use terbinafine or itraconazole. When the disease is extensive, combination therapy with flucytosine plus itraconazole is of potential use.

### Other subcutaneous mycoses

The other subcutaneous mycoses are even rarer and occur in remote areas. It is not possible to provide an evidence base for their diagnosis and treatment. They include the subcutaneous mucoromycete infections due to *Conidiobolus* and *Basidiobolus* species, which cause woody swellings infiltrated by the strap-like fungi that cause the infections, fibroblasts, and eosinophils.

### Systemic mycoses

The systemic mycoses occasionally exhibit direct skin invasion following infiltration of organisms, or indirect skin manifestations such as erythema nodosum or multiforme, which are thought to develop following immune complex deposition. These are discussed briefly below.

#### Key points: chromoblastomycosis

- Chromoblastomycosis is caused by a number of different environmental fungi that are implanted through the skin.
- On the basis of several case series, most infections probably respond to terbinafine or itraconazole.
- Physical therapies such as cryotherapy and heat treatment have also been used and may confer additional benefit to drug therapy.
- Flucytosine plus itraconazole may be of value in people who have extensive disease.

### The endemic mycoses

Skin involvement is seen as a consequence of one of three different mechanisms: direct penetration, bloodstream spread from a deep focus, and as an immunological reaction to primary, often respiratory, infection. In the latter instance, the skin lesions most commonly seen are erythema nodosum or multiforme.

In the endemic mycoses, the usual portal of entry is the lung. Direct entry via inoculation has been proposed in the case of some mycoses, such as paracoccidioidomycosis caused by *Paracoccidioides brasiliensis*, in which mucocutaneous lesions are common (for example, around the nose or mouth). The incidence of pulmonary disease in *P. brasiliensis* infection, even in the presence of skin lesions, is much higher in the endemic areas, suggesting that widespread subclinical exposure is most likely acquired through the airborne route. The demonstration of dissemination to mucocutaneous areas following fungemia in animal models and the existence of subclinical pulmonary forms of disease support the view that skin lesions of paracoccidioidomycosis result from dissemination to skin from the lung. This is likely to be true of most cases of systemic endemic mycosis.

### Opportunistic mycoses

The opportunistic mycoses include infections due to *Candida*, *Aspergillus*, and zygomycete fungi of the genera *Rhizopus*, *Rhizomucor*, and *Absidia*, amongst others. Infection affecting the skin is uncommon, and these infections seldom present to a dermatologist; any skin involvement has to be set against the background of widespread and life-threatening disease. These infections often occur in patients with severe defects of either neutrophil numbers or function, such as recipients of stem cell transplants and cancer patients. *Candida* also affects seriously ill patients in intensive care or after abdominal surgery, neonates, and after prolonged intravenous feeding. Isolated cases of cutaneous aspergillosis and zygomycosis have been recognized following abrasion at a specific site. Disseminated candidosis rarely affects the skin either in neutropenic individuals or in intravenous drug abusers. Systemic *Cryptococcus* infection has been extensively evaluated in at least 16 randomized controlled trials in people with AIDS.

Patients with deep systemic mycoses rarely present directly to the dermatologist. However, there is an extensive literature on the treatment of disseminated fungal infection, and through the involvement of organizations such as the Mycosis Study Group (USA), the UK Medical Research Council (MRC), and the European Organization for the Research and Treatment of Cancer (EORTC) a number of ground-breaking controlled clinical trials have been undertaken independently of, but with full cooperation from, the pharmaceutical industry. These have focused on various forms of treatment, from prevention to specific therapy or empirical therapy.

One form of systemic mycosis that a dermatologist may be called to see is primary cutaneous cryptococcosis. Proving the existence of genuine isolated cutaneous forms of disseminated fungal disease following local trauma and possible direct inoculation, in comparison with localized lesions following bloodstream spread, has been difficult, but the concept is important as it has implications for treatment (for example, the use of smaller doses that might be effective in localized forms of infection). The problem is well encapsulated by consideration of primary cutaneous cryptococcosis.

Cases of primary cutaneous cryptococcosis are rarely reported, and the evidence for direct entry through the skin is often poorly substantiated and generally anecdotal. There are no clinical signs that are likely to provide an accurate indicator that the infection has developed as a result of cutaneous inoculation [42]. The evidence for its occurrence, therefore, can be summarized as follows:

- The first sign of infection is the development of an isolated skin lesion.
- There are no other signs or symptoms of disease, apart from regional lymphadenopathy.
- There is no circulating cryptococcal antigen or antigen in the cerebrospinal fluid, measured by conventional tests such as the cryptococcal antigen enzyme-linked immunosorbent assay.
- Oral antifungal therapy with fluconazole or itraconazole is effective.

An alternative interpretation for the development of cryptococcal skin lesions was described some time ago by Noble and Fajardo [43] and was based on the subsequent identification of another focus of infection (for example, lung, prostate) and evidence of positive serology in blood or cerebrospinal fluid [44,45]. This suggests that many cases of cutaneous cryptococcosis are not primary skin lesions at all, but result from fungemia [46,47]. In some cases, this process produces only a single skin lesion.

Examination of the literature shows that there are some patients who meet the criteria for primary cutaneous cryptococcosis [42].

These are generally elderly individuals who do not have any underlying condition known to predispose to cryptococcosis (AIDS, sarcoidosis, T cell lymphoma, or chronic oral steroid therapy). Often, they give a history of local skin injury, sometimes even associated with a peck by a bird that might be carrying *Cryptococcus*. Often, strains isolated from such lesions belong to *Cryptococcus neoformans* serotype D [48]. In AIDS patients, cutaneous cryptococcal infections may also be superimposed on some other process such as Kaposi's sarcoma [49] and are really part of a disseminated infection.

It is important to emphasize that these are observed criteria and have not, by virtue of the rarity of cutaneous cryptococcosis, been subjected to analysis of sufficient scientific rigor. However, the implications for therapy are sufficiently important that it is recommended that patients who meet the broad criteria for primary cutaneous cryptococcosis, after rigorous investigation to exclude disseminated disease, receive treatment with an oral azole antifungal agent, such as fluconazole (at least 200 mg daily) or itraconazole (at least 200 mg daily) until the lesions have resolved, treatment being extended for at least 1 month thereafter. Serology should be monitored again before the end of treatment and for 6 months after the end of treatment. This approach is provided as a guideline based on anecdotal experience and has not been the subject of a clinical trial.

### Key points: systemic mycoses

- Systemic mycoses are not usually treated primarily by dermatologists.
- Most opportunistic mycoses are seen in immunocompromised patients.
- Skin lesions in most endemic mycoses, such as paracoccidioidomycosis, probably result from lung dissemination.
- They occasionally exhibit direct skin invasion following infiltration of organisms, or indirect skin manifestations such as erythema nodosum or multiforme, probably from immune complex deposition.
- Although many patients with cutaneous cryptococcal infection probably develop skin involvement as a result of internal spread, some cases of primary cutaneous cryptococcus do exist.
- Anecdotal evidence suggests that itraconazole or fluconazole might be effective in such cases.
- A number of controlled clinical trials on the treatment of systemic mycoses are currently being conducted by the US Mycosis Study Group, the MRC and the EORTC.

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# Streptococcal cellulitis/erysipelas of the lower leg

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## Background

### Definitions and etiology

Cellulitis is inflammation due to infection of the superficial and deep dermis. It is characterized by local heat, erythema, induration, or pain in the affected area. Cellulitis can occur in any area, but it occurs most commonly on the lower extremities. Erysipelas is a spreading infection of the superficial dermis. In practice, these may coexist. Use of the term “erysipelas” to describe spreading mid-facial streptococcal infection is universal, but the same infection in the lower leg may be termed cellulitis (in the UK and USA) or erysipelas (in Europe).

Cellulitis occurs in many situations and due to many organisms. In most studies from dermatology departments, the lower leg is the main site of involvement (75% to over 90%), and most cases are streptococcal. Even amongst unselected or emergency department patients, the lower leg usually accounts for about two-thirds of cases. Proving streptococcal etiology is difficult. Staphylococcal infection is the most important differential diagnosis at this site.

This chapter focuses on cellulitis of the lower leg (Figure 46.1), and on the clinically important questions on its management.

### Clinical features

Typically, streptococcal cellulitis is initially manifest as swelling of the forefoot, accompanied or preceded by general malaise and/or fever [1–4]. It progresses as proximally spreading, confluent, tender erythematous swelling accompanied by malaise, fever, and often rigors. Swelling and pain may be severe; blistering, lymphangitis, and/or lymphadenopathy may occur. Although it is often used as a diagnostic criterion, significant pyrexia may be absent in more than half of patients admitted to hospital [5,6].

### Incidence/prevalence

No accurate data are available. The incidence is overestimated if other infections are classified as cellulitis, or underestimated if cellulitis treated in the community is not included. Abscesses or localized wound infections, and/or cellulitis at other body sites, are often included in incidence/prevalence data.

Cellulitis and abscesses accounted for 158 consultations per 100 000 person-years at risk in the UK in 1991, and skin and subcutaneous infections resulted in 29 820 hospital admissions that year [7], but these data are not specific to cellulitis of a pattern relevant to this chapter. In a UK district general hospital, about 3% of admissions were for cellulitis [8]. Incidence data from UK hospitals reveal 69 576 episodes of cellulitis and 516 episodes of erysipelas in 2004–2005 [8].

### Importance and prognosis

In those with severe symptoms such as high fever, blistering, severe pain, or lymphadenitis, or in whom systemic features resolve with antibiotics but redness and swelling persist, hospital admission is usually recommended. In those who do require admission, numerous studies [4,9,10] and UK National Health Service data (cited in Pearse *et al.* [7]) document a mean duration of stay of 9–10 days. Recent data from the UK National Health Episode Statistics show a trend toward shorter mean durations of 5–6 days, representing a significant decrease in health-care costs [11]. Uncommonly, cellulitis may progress to sepsis, necrotizing fasciitis, or streptococcal toxic shock syndrome, each of which has significant mortality.

In addition, long-term sequelae such as persistent edema, leg ulceration, or further episodes are all common (see the section on long-term complications below). Morbidity is therefore significant.

### Diagnostic tests

The diagnosis of cellulitis is largely based on clinical features of localized swelling and erythema of the skin, accompanied or preceded by general malaise or fever. Streptococci may be identifiable by culture of swabs from macerated toe webs, blister fluid, or ulceration (but leg ulcers, if preceding cellulitis, may be colonized with numerous bacterial species). Aspiration or skin biopsy may yield positive cultures; streptococcal antigen identification by direct immunofluorescence of skin biopsies or using latex agglutination increases the diagnostic rate but is not routinely performed.

Analysis of the results of cultures in six studies (including 284 patients) documented a causative organism in 29% of cases [3]. One





**Figure 46.1** Streptococcal cellulitis of the leg: marked erythema, edema, and early blistering.

study (229 patients, 79% with leg cellulitis) using cultures and antistreptolysin-O titers (ASOTs), isolated group A streptococci from a relevant skin site in 19%; ASOT was elevated acutely in 30%, but more commonly (61%) in convalescent sera [12]. If a relevant organism is identified in the ascending lower leg pattern of cellulitis, streptococci of group A (less frequently group G) account for about 80% of isolates. One review of 808 patients with cellulitis of intact skin (of any body site) with positive needle aspiration or punch biopsy skin cultures demonstrated a causative organism in 16% of cases, with *Staphylococcus aureus* as the most common etiologic agent (accounting for 50% of positive cultures), drawing attention to the need for heightened clinician awareness of local epidemiologic patterns of incidence and resistance in community-acquired bacterial infections of the skin [13].

The growing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is also manifested by an increasing frequency of this organism as a common cause of cellulitis. Of 384 patients with community-acquired staphylococcal skin or soft tissue infections seen in a large urban hospital in the USA, 72% were caused by MRSA [14].

### Aims of treatment

- To resolve symptoms, reduce the duration of hospital admission, and avoid or reduce sequelae such as edema.
- To prevent subsequent episodes.

### Outcome measures

- Resolution of fever/malaise, erythema, edema (or halting progression of erythema; see the discussion below). The “NICE CKS” guidelines – a series of evidence-based clinical knowledge summaries developed by the UK National Institute for Health and Clinical Excellence for the care of patients in primary care settings – cite cure at 14 days as a suitable outcome measure [15].
- Elimination of risk factors, especially tinea pedis if relevant as a portal of entry.

### Methods of search

A search was carried out using “cellulitis” or “erysipelas” in the Cochrane Database of Systematic Reviews, Medline, and Embase databases up to May 2007. A search for new updates to the literature was performed in November 2012.

Key case series and interventional studies were identified from references obtained and from the authors’ files. A Cochrane review on the subject of interventions for cellulitis and erysipelas was published in 2010.

## Questions

### What are the factors that predispose to lower-leg cellulitis?

#### Evidence summary

The clinical diagnosis of cellulitis relies on recognition of localized swelling and erythema that, in the appropriate clinical context, suggest a bacterial infection. When patients clinically diagnosed with cellulitis are compared with matched control subjects, several factors have been identified associated with an increased risk of cellulitis. Lower-leg lymphedema and venous insufficiency have been identified as predisposing factors associated with the development of lower-leg cellulitis. The presence of disrupted skin integrity, compromising the barrier function of the skin and thus providing a portal of entry for microbial species, is also consistently linked with patients with cellulitis more frequently than control subjects. The presence of interdigital toe web-space infection such as tinea pedis has been variably identified as a risk factor, likely also due to associated barrier dysfunction. Obesity – with or without the presence of lower-extremity edema – and diabetes mellitus have also been identified in selected studies as risk factors for the development of cellulitis.

#### Case-control studies

Patients admitted to the hospital with lower-leg cellulitis ( $n = 167$ ) were compared with controls ( $n = 294$ ; matched for age, sex, and hospital) across seven hospital centers. Lower-leg cellulitis or erysipelas was defined as the sudden onset ( $<24$  h) of a well-demarcated cutaneous inflammation, with fever  $>38^\circ\text{C}$  or chills. Patients under 15 years of age and patients with abscess or necrotizing fasciitis were excluded from analysis. One dermatologist in each study center conducted direct interviews with a structured questionnaire and clinical examination of cases and controls with regard to risk factors for cellulitis. Risk factors were lymphedema, odds ratio (OR) of 71.2 (95% confidence interval [CI], 5.6–908), presence of a portal of entry (toe web intertrigo, ulcer, wound, dermatosis) (OR, 23.8; 95% CI, 10.7–52.5), venous insufficiency (OR, 2.9; 95% CI, 1.0–8.7), leg edema (OR, 2.5; 95% CI, 1.2–5.1), and being overweight (OR, 2.0; 95% CI, 1.1–3.7) [16]. Diabetes (identified as a risk factor in some smaller studies) showed no association with the occurrence of cellulitis. Toe web disease was present in 66%, leg edema in 38%, and lymphedema in 18%.

A total of 100 patients were compared with 200 age-matched and sex-matched control individuals, with an emphasis on toe web disease, and using both questionnaires and clinical examinations [17]. Inclusion criteria for case patients were (1) presence of lower-limb cellulitis and (2) the absence of abscess formation or necrotizing fasciitis. Lower-limb cellulitis was defined as a demarcated cutaneous inflammation of sudden onset of less than 72 h duration that was associated with fever, chills, or leukocytosis. The investigators completed a questionnaire for each patient, examined both lower extremities, and skin and toenail samples were obtained from the affected limb to assess for tinea pedis or bacterial infection. Risk factors for cellulitis were previous cellulitis (OR, 31.04; 95% CI, 4.15–32.2), staphylococci or streptococci in the toe webs (OR, 28.97; 95% CI, 5.47–153.48), leg erosions or ulceration (OR, 11.80;

95% CI, 2.47–56.33), and prior saphenectomy (OR, 8.49; 95% CI, 1.62–44.52). Toe web tinea infection was only associated when toe web bacterial infection was excluded from analysis (OR, 3.86; 95% CI, 1.32–11.27) [17].

In a study of 114 Tunisian patients with erysipelas of the leg compared with 208 controls matched for age, sex, and hospital-of-care, direct physician-led interviews and physical examinations were performed to assess risk factors [18]. No laboratory investigations were performed. Significant risk factors identified via multivariate analysis included cutaneous barrier disruption of the lower extremity (OR, 13.6; 95% CI, 6.3–31.0) and the presence of leg edema (OR, 7.0; 95% CI, 1.3–38). None of the general risk factors – being overweight, smoking, sedentary work, alcohol consumption, or diabetes mellitus – were associated with increased risk of lower-extremity erysipelas [18].

### Retrospective studies

Patients with recurrent cellulitis were compared with a group with single episodes (total  $n = 574$ , 81% of which involved the leg, with a retrospective single-institution analysis). Risk factors for recurrence (all statistically significant) were being overweight, venous insufficiency, lymphedema, tinea pedis, and previous regional surgery or trauma [19].

In a case-note review with questionnaire follow-up at up to 3 years after admission, it was found that, of 171 patients, 47% had a history of recurrent episodes and 46% had chronic edema. These two sequelae were strongly associated ( $P = 0.0002$ ) [20]. Chronic edema specific to, or greater in, the post-cellulitis lower leg was identified by 37%. Thirteen percent of the patients had leg ulceration attributed to cellulitis.

In a study of 243 patients and 467 control individuals (matched for age  $\pm 5$  years, sex, hospital, and timing of admission), mycologically proven foot dermatomycoses of various types were found to be the major risk factor for bacterial cellulitis (overall OR, 2.4; interdigital tinea OR, 3.2). Other associations with cellulitis were other portals of entry, a history of previous cellulitis, chronic venous insufficiency, and leg edema [21].

In 647 patients with cellulitis/erysipelas (91.2% in the leg), general or local risk factors were found in 26% (interestingly, only 3.3% had leg edema). Seventy-seven percent of the patients had portals of entry, 50% of which were (predominantly toe web) fungal infections [10]. In a study of 30 patients with lower extremity cellulitis, 13 out of 15 patients (87%) assessed by lymphoscintigraphy had evidence of abnormal lymphatic circulation in the involved lower extremities, with eight of the 15 (53%) demonstrating bilateral lower extremity abnormalities [22].

In 365 patients with cellulitis (76% in the leg), 24% had fungal infections, described as “mostly tinea pedis.” Accurate figures cannot be extracted from the data, but this represents approximately one-third of those with leg cellulitis having tinea pedis [23].

About a quarter of patients with lymphedema will have at least one episode of cellulitis or related skin infection in the affected limb(s), potentially with recurrences every few weeks, and probably with a higher frequency in those in whom the cause is not related to cancer treatment; although cited in a Cochrane review, this is based on unpublished original data. It is not clear that all such inflammatory episodes are truly infective [24].

### Comments

The publications documenting risk factors for lower leg cellulitis probably represent the strongest evidence in this chapter, with con-

sistent results implicating chronic edema (venous or lymphedema), toe web bacterial and/or fungal infection, and obesity as major risk factors. The importance of distinguishing lymphatic from venous edema may be artificial; the two are typically combined once chronic [25], leading to the use of the term “lymphovenous edema.” As a risk factor for cellulitis, it is not clear whether it is the chronicity or severity of edema, or both, that is important. It is important to be aware that cellulitis is not only a consequence of edema, but that it also causes chronic edema, so that there is a vicious cycle leading to further episodes [20,26]. The effect of therapy to address these risk factors needs to be assessed.

Other predisposing factors for cellulitis include intravenous (IV) drug abuse and conditions in which blood vascular anomalies are associated with lymphatic abnormality (e.g., Klippel-Trénaunay syndrome).

## What is the best antibiotic treatment regimen?

### Evidence summary

Antibiotic treatments for cellulitis remain a focus of ongoing clinical research and evidence-based review. A recently completed Cochrane review of treatments for cellulitis and erysipelas provides the most comprehensive assessment to date of therapeutic interventions [27]. The Cochrane review included 25 studies covering 2488 patients with cellulitis. The heterogeneity of study designs and treatment variables (no two studies compared the same two antibiotic treatment regimens) limited the ability to make definitive recommendations following review of the data. The writing group was unable to define the best treatment for cellulitis. However, the reviewers concluded that the limited evidence of three trials [28–30] suggested macrolide and streptogramin antibiotics are slightly better than penicillins for reducing symptoms at the end of antibiotic treatment for cellulitis.

Pertinent clinical questions regarding antibiotic treatment regimens include the specific therapeutic agent, the mode of administration, and the duration of treatment. Previous evidence-based reviews have found no satisfactory randomized studies of antibiotics versus placebo or of IV antibiotics versus the same agent given orally [8], although one such study exists for IV versus intramuscular (IM) administration of penicillin [31]. There are some published summaries of head-to-head comparisons. Most show no difference between the active agents compared [4,32].

The following studies have been chosen as they address specific pertinent issues. Antibiotics used in home treatment programs are discussed later.

### Prospective studies

One randomized controlled trial (RCT) of 81 patients with lower-leg cellulitis compared flucloxacillin alone versus flucloxacillin in combination with benzylpenicillin. This study showed no difference between the two regimens with regard to the number of doses required (mean number of doses, 8.71 for flucloxacillin alone and 8.47 for the dual regimen; mean difference,  $-0.24$  doses; 95% CI for the difference,  $-2.38$  to  $-2.01$ ;  $P = 0.83$ ), next-day temperature (mean difference,  $-0.07^\circ\text{C}$ ; 95% CI,  $-0.76$  to  $-0.62$ ;  $P = 0.84$ ), or area of erythema decrease (mean difference,  $-34\text{ mm}$ ; 95% CI,  $-99$  to  $-31$ ;  $P = 0.30$ ). Pain scores and patients' subjective improvement scores were also similar in the two groups. Overall, this study did not support the addition of benzylpenicillin to flucloxacillin [33].

Another RCT investigating IV benzylpenicillin 4 MU six times daily ( $n = 55$ ) in comparison with IM penicillins (a mixture of benzyl penicillin and procaine penicillin) 2 MU twice daily ( $n = 57$ )

assessed cure rates and local complication rates in the two groups. Recovery was defined by a score of zero for erythema, edema, and pain and by a normal temperature on the 10th day of treatment or before. Patients who showed local or general state complication during the 10 days of treatment or who did not have clinical improvement at the 10th day of treatment were considered treatment failures and left the trial. The investigators found no difference in the cure rate (failure rate 14% IM, 20% IV; absolute risk difference 6%,  $P = 0.40$ ) or local complications (9.1% IV, 7% IM;  $P = 0.477$ ), but 26% had venous inflammation in the IV group [31]. The IV and IM routes were thus equally effective, but there was less treatment-related morbidity with IM penicillin.

A third RCT screened 169 patients with cellulitis, 48 of whom were excluded (exclusion criteria included neutropenia, abscess formation, deep infection, incorrect diagnosis, confined to area of a bite, diabetic foot infections, others). All 121 participants received 5 days of levofloxacin 500 mg/day and were then assessed; 87 were randomly assigned to either a further 5 days of treatment ( $n = 43$ ) or 5 days of placebo ( $n = 44$ ). Participants were excluded from day 5 randomization if they had worsening cellulitis, no improvement, positive blood culture, ulceration, an alternative diagnosis (e.g., bursitis), abscess, or another nidus of infection. Both groups achieved 98% success (clearance by 14 days, no relapse within 28 days) [34].

A parallel-group open trial of 289 patients with erysipelas (cellulitis) compared oral pristinamycin versus IV and then oral penicillin; 102 patients in each limb were able to be assessed for the primary end point (cure rate at 24–25 days). Exclusions were mainly for protocol violations (additional therapy, missed therapy, missing data). Both drugs have a high level of antistreptococcal activity. The cure rates (per protocol and intention to treat) were 81% and 65% for pristinamycin in comparison with 67% and 53% for penicillin, both statistically significant differences (per-protocol absolute risk difference, 14%; 97.06% CI, 3.3% to  $\infty$ ; intention-to-treat absolute risk difference, 12%; 97.06% CI, 1.7% to  $\infty$ ) [28]. Adverse effects included a higher frequency of (usually nonlimiting) gastrointestinal symptoms with pristinamycin.

Recent attention has focused on treatment of cellulitis with regimens providing adequate coverage for MRSA in light of the organism's increasing prevalence. A randomized, evaluator-blinded, multicenter trial of 103 patients with cellulitis or erysipelas requiring hospitalization compared treatment with IV daptomycin versus IV vancomycin; mean treatment durations were 6.1 days and 6.2 days, respectively. 32.0% of daptomycin- and 35.3% of vancomycin-treated patients in the study reported a previous episode of cellulitis or erysipelas within the prior 5 years. The clinical success rate for complete clearance or improvement, judged 7–14 days after the final dose of antibiotic, was comparable for both treatments, at 94.0% for daptomycin versus 90.2% for vancomycin [35].

### Retrospective studies

In 365 patients (76% lower leg site), penicillin alone was used in 45%. Other antibiotics were significantly more frequently used in those with predisposing conditions or in those who were hospitalized. (Patients with bullous cellulitis or with streptococcal toxic shock syndrome were excluded.) The authors documented a median hospital stay of 5 days in the "penicillin alone" and the "other antibiotics" groups, but a longer maximum stay in the "other antibiotic" group (28 vs 20 days) and an overall statistically different mean duration of stay [23]. The "other antibiotic" group also had a higher rate of predisposing conditions. The authors concluded that there is no advantage with the use of antibiotics other than penicillin.

### Comments

The most comprehensive review of the evidence to date on the topic of treatment for cellulitis (the Cochrane review completed in 2010) provides insight into the challenge of determining the therapeutic regimen for management of this condition [27]. The reviewers were not able to identify the best treatment for cellulitis based on the review of the current literature.

While macrolide and streptogramin antibiotics may provide better efficacy than penicillin antibiotics for symptom reduction, several studies have validated the role of penicillins as a treatment of streptococcal cellulitis. Benzylpenicillin or phenoxymethylpenicillin have a very low minimal inhibitory concentration (MIC) against streptococci, excellent response rates in most streptococcal disease, and a very low and unchanging (over many decades) risk of streptococcal resistance [36–38]. The main reservations about the use of penicillin alone are cases of nonstreptococcal etiology.

Flucloxacillin alone has been recommended as first-line therapy for cellulitis by guidelines such as those of the Clinical Resource Efficiency Support Team (CREST) [39] and NICE CKS [15]. The Infectious Diseases Society of America recommends penicillin for erysipelas (well-demarcated tender plaque) and a penicillinase-resistant penicillin or first-generation cephalosporin for cellulitis, although they also state that most cellulitis is streptococcal (staphylococcal infection being rare unless associated with an underlying abscess or penetrating trauma) [40].

The increasing prevalence of MRSA, especially as a cause of abscesses and other cutaneous infections, has led to the statement that the evidence used in creating current guidelines for the treatment of skin and skin structure infections has significant limitations, especially as many studies have used comparative noninferiority protocols [41]. Further systematic review of therapeutic interventions for the treatment of MRSA cellulitis and skin infection is warranted for this increasing public health challenge.

### Where should patients be treated?

#### Evidence summary

Most studies of cellulitis have been conducted in secondary care facilities. The number of patients previously treated in primary care is unclear. The possibility of making a definitive choice for treatment at home has been assessed recently as another locus of clinical care delivery. Randomized trials allocating patients to either home or inpatient care contain several methodological constraints regarding patient selection. Several innovative models of home therapy are currently being explored. The very limited rigorously designed studies on this topic suggest that home treatment for cellulitis may have the potential to yield similar clinical outcomes for a selected population of patients.

#### Prospective studies

One RCT was undertaken in patients perceived to have cellulitis requiring IV antibiotics and with no contraindication to home therapy (home,  $n = 98$ ; hospital,  $n = 96$ ) [42]. There were no significant differences in the time to the primary end point, cessation of advancement of erythema (mean, 1.50 days with home treatment and 1.49 days in the hospital group; mean difference,  $-0.01$  days; 95% CI for the difference,  $-0.3$  to  $-0.28$ ), or in the days on IV antibiotics (cephazolin at home; various others also used in hospital), days on oral antibiotics, overall days of treatment, complications, pain, or function; home treatment was preferred. However, there were several exclusion criteria, including previous cellulitis at the same site within 1 month, neutropenia or neutrophilia, signs of



sepsis, comorbidities (“severe” diabetes, obesity, peripheral vascular disease, alcoholism, immunosuppression), directly cellulitis-associated factors (such as blistering, tissue necrosis, severe lymphangitis, or a large area of cellulitis), or refusal to enter the trial. In order to randomly assign 200 patients (into groups of 101 and 99, with 10 rediagnosed after randomization), 658 patients fulfilling the entry criteria had to be screened (thus, only 30% of the potential patients actually entered the trial).

### Retrospective studies

A total of 266 episodes of cellulitis treated in a hospital-initiated “hospital-in-the-home” program were reviewed. After accounting for some miscoding (six episodes of ongoing cellulitis, 18 cases of pilonidal sinus), the length of stay was similar in the home and hospital groups (mean, 7.3 days at home and 7.1 days in hospital) [43].

In a review of 124 patients with cellulitis who were considered suitable for home IV therapy in accordance with local “hospital-in-the-home” guidelines [44], the exclusion criteria included children, bites, deep involvement or surgical review necessary, signs of severe systemic illness, leukopenia, or white cell count  $>20 \times 10^9/L$ . Two-thirds of the patients had cellulitis of the leg; over 99% were treated with cephazolin 2 g twice daily. Eighty-five percent were treated successfully with a mean IV antibiotic duration of 6.24 days. The published details are insufficient for separate analysis of the lower-leg subset.

A study compared 112 patients with “uncomplicated cellulitis” and 230 retrospective control individuals to determine the benefits of a protocol for baseline suitability for treatment at home, with recording of symptoms and signs by nurses and criteria for medical review [45]. Most home treatment was initially once-daily IV ceftriaxone, then 7 days of oral clindamycin or flucloxacillin. Using a protocol led to a reduction in the median duration of IV antibiotic therapy (3 days, vs 4 days in the pre-protocol controls), and reduced physician review (19% vs 100%), but the outcomes, complications, and readmissions were similar. Exclusions, which were also applied to the control group by examination of case records, included severe localized pain, rapid evolution, blistering, hypotension or other features of sepsis, drug or alcohol misuse, some patients with wounds or trauma, and social factors that would make home treatment difficult. The number of exclusions was not stated, but of those entering the home treatment program, 36% had had an immediately preceding hospital admission for their cellulitis (45% in the retrospective controls).

An alternative to home IV antibiotic treatment is early discharge once IV therapy is no longer considered necessary. In a retrospective study, 17% of 374 patients were discharged on the same day as IV antibiotics were stopped, rather than having a further in-patient night for observation [46]. Although only 40 (15%) in this series had cellulitis, none of these had significant pyrexia or local symptom recurrence on the final “observed” or “unobserved” day and none required readmission within 14 days.

A retrospective analysis of 334 episodes of outpatient parenteral antibiotic therapy (OPAT) in the UK included 198 episodes of cellulitis or erysipelas, all but one treated with IV ceftriaxone. Patients received antibiotics either at local infusion centers or self-administered (or administered by a family member or carer) at home. A cure rate of 92% at the end of treatment (mean duration of treatment with IV antibiotics was 7.04 days) was assessed by specialist nurses for the patients with skin infections. The authors calculated 972 inpatient hospital bed-days for skin infections were

saved by OPAT treatment of cellulitis and estimated significant cost savings from care in the outpatient program compared with inpatient hospitalization for the same diagnosis [47].

### Comments

All of these studies suggest that treatment at home is safe and effective, especially if supported by a carefully prepared protocol. However, all need to be interpreted with caution; all of the studies involved decisions about patients’ suitability for home treatment and excluded patients with more severe disease or with factors precluding home therapy. None, therefore, represents an RCT of unselected subjects. In one large retrospective review of 647 patients with cellulitis (91% leg), only 27% were felt to require hospitalization, with a mean duration of stay of 9 days [10]. However, the one prospective study [42] was only able to recruit 30% who fulfilled the criteria for needing IV therapy. The number of screened but excluded subjects is not apparent in all of the above studies, but the available data suggest that a minority of patients who would normally require admission can actually be treated at home.

In addition, some of the end points used have uncertain clinical relevance. “Cessation of advancement of erythema” is an end point that appears appropriate, but some hospital admissions are for patients in whom “erythema is not resolving.” Indeed, this condition – sometimes (probably incorrectly) termed “chronic cellulitis” – is thought by many to represent an ongoing immunological response to infection [34], although, particularly if bilateral, it may just represent background lymphedema. The important point is that it is not an end point that automatically excludes subsequent hospital admission.

Early discharge after IV antibiotics does not appear to be associated with a greater risk of adverse events [46], but there was a bias in that patients who were discharged on the day on which IV antibiotics were stopped were younger and had fewer comorbidities. Home antibiotic treatment may also offer a lower cost of care than inpatient admission, suggesting an opportunity for shared savings in the management of patients with cellulitis.

### What factors are associated with or predict short-term morbidity, severe disease, or mortality, and what tests should be done?

Short-term complications of cellulitis include severe edema, blistering, leg ulceration, abscess formation, unrecognized infection by rare organisms, necrotizing fasciitis, septicemia, streptococcal toxic shock syndrome, and death. Severe complications are, however, rare. Clinical features that suggest necrotizing fasciitis are discussed elsewhere [1,48–50]; laboratory tests that may be useful in this diagnosis or that of streptococcal toxic shock syndrome (the two are commonly associated) are presented as they are pertinent to the question of “what tests should be done?”

Abbreviated criteria for streptococcal toxic shock syndrome (see Bisno and Stevens [1] for more detailed criteria and a definition of “definite” or “probable” case) include:

- 1 Isolation of group A streptococci.
- 2 Signs of severity:
  - i hypotension (systolic blood pressure  $<90$  mmHg);
  - ii two or more of:
    - renal impairment (creatinine  $>177 \mu\text{mol/L}$ ) or  $>2\times$  upper limit of normal for age;
    - coagulopathy (platelets  $<100 \times 10^9/L$  or evidence of disseminated intravascular coagulation);



- liver involvement – transaminases or bilirubin  $>2\times$  upper limit of normal for age;
- adult respiratory distress syndrome/capillary leak syndrome;
- generalized macular rash;
- soft-tissue necrosis (includes necrotizing fasciitis, myonecrosis, gangrene).

A clinical suspicion of necrotizing fasciitis (especially “crescendo” pain, tender induration, pallor, or cyanosis superimposed on erythema, crepitus, lack of lymphangitis, hypoesthesia, foul exudates, muscle pain or weakness, and increasing systemic symptoms – e.g., fever, confusion, hypotension) should prompt consideration of laboratory evaluation of renal function, coagulation factors, and liver involvement, as well as surgical assessment. Bullae may occur in either “ordinary” cellulitis or in more severe infection; severe pain often precedes skin signs in necrotizing fasciitis [50], and bullae, when they appear, are often on a background of vague dusky discoloration rather than of acute erythema [48].

### Evidence summary

A systematic review of blood cultures in patients with cellulitis reveals that they are infrequently positive, with a causative organism identified in fewer than 10% of cases. When organisms are present, however, tailored antibiotic therapy may be achievable. Retrospective data reveal a low likelihood of death from cellulitis. No single diagnostic test appears superior for predicting prognosis of patients with cellulitis, but elevated markers of systemic inflammation suggest an increased risk of adverse outcomes.

### Systematic review

A review of 17 retrospective studies or case series of nonfacial cellulitis [51] found that blood cultures were usually negative, and if positive did not alter the empirical therapy already commenced. On the basis of the studies reviewed, the frequency of positive blood cultures in uncomplicated cellulitis is about 2–5%. A recently completed systematic review of 28 studies with reported blood culture data in 2185 patients with cellulitis or erysipelas found 4.6% of 607 patients with erysipelas and 7.9% of 1578 patients with cellulitis had positive culture results [52]. In these patients with erysipelas with positive blood cultures, 46% were *Streptococcus pyogenes*, 29% were other  $\beta$ -hemolytic streptococci, 14% were *Staphylococcus aureus*, and 11% were Gram-negative organisms. For cellulitis, 19% of positive cultures grew *Streptococcus pyogenes*, 38% were other  $\beta$ -hemolytic streptococci, 14% were *Staphylococcus aureus*, and 28% were Gram-negative organisms [52].

### Prospective studies

We found no prospective studies.

### Retrospective studies

In one study [23], there were no deaths amongst 365 patients, although those with bullous cellulitis were excluded, as were an unspecified number with streptococcal toxic shock syndrome (a condition with a mortality rate of 50%).

In a single-institution analysis of risk factors for poor outcome in 332 adults with cellulitis [53], the body sites were not stated, but localized cellulitis of the orbit and infections related to surgical wounds, diabetic foot ulcers, or IV drug use were excluded. Death occurred in 16 (5%) within 1 month (including eight, 2%, within 72h), and was statistically associated with male sex, congestive

cardiac failure, morbid obesity, any two comorbid conditions (diabetes, cancer, cirrhosis, congestive cardiac failure, chronic obstructive pulmonary disease, morbid obesity, or HIV infection), shock, hypoalbuminemia, elevated creatinine ( $>150\mu\text{mol/L}$ ), and *Pseudomonas* infection (which accounted for five of the 16 deaths).

In the same study [53], complications in 103 patients (31%) included a need for surgical debridement or other surgery (29%), shock (4.5%), or other systemic complications (11.5%). Although not significantly associated with death, an absence of necrosis at presentation was significantly linked with early discharge without complications.

In a review of 647 cases, 91% affecting the leg, only one patient developed necrotizing fasciitis (although only 176 of the patients in this series were felt to have sufficient severity of disease that admission was necessary) [10].

In a series of 229 patients (79% with a leg site), 14% had local skin necrosis or abscess, but none developed streptococcal toxic shock syndrome [12].

In 200 patients with soft-tissue infection (66% affecting the leg), the mean C-reactive protein and erythrocyte sedimentation rate at admission were significantly higher in the group requiring more than 10 days’ admission in comparison with those discharged earlier [54].

A retrospective analysis of 395 episodes of cellulitis or erysipelas (74% affecting the lower leg) requiring hospitalization at a single institution over an 8-year period was reported in 2010 [55]. Patients with local complications, such as abscess or bursitis at presentation, were excluded, as were those with deep infection or a diagnosis of necrotizing fasciitis. The analysis found an overall mortality of 2.5% and the development of systemic or local complications in an additional 28.4% of patients. Multivariate analyses identified preexisting congestive cardiac failure, neutrophilia/penia within 24h of admission, albumin  $<30\text{g/L}$ , purulent discharge from the cellulitic area, altered mental status, and the presence of bacteremia as factors associated with an increased odds of adverse outcomes (local or systemic complications or death). A five-point scoring system was constructed by the study’s authors to stratify patients at high risk of adverse outcomes on presentation based on 198 randomly selected patients and was validated using the other 197 in the study; the scoring system assigns five points for altered mental status, and two points each for congestive cardiac failure, discharge from cellulitis site, hypoalbuminemia, and neutrophilia/penia, with scores below 4 having a low risk of adverse outcomes. Hospital stays longer than 7 days were necessary in 35.1% of patients. Factors associated with an increased odds of long hospitalization included age over 60, albumin  $<30\text{g/L}$ , symptoms for more than 4 days, bacteremia, and MRSA identified as the causative agent [55].

Data regarding the incidence of superficial and deep venous thromboses in cellulitis or erysipelas of the lower extremities reveal they are relatively infrequent complications. The incidence across studies in which a systematic investigation for deep venous thrombosis was performed (eight studies involving 990 patients) using Doppler ultrasonography, venography, or fibrinogen-uptake test was calculated as 2.7% (95% CI, 1.71–3.73%) [56].

In a retrospective study of 43 cases of necrotizing fasciitis [57], streptococcal necrotizing fasciitis was more likely to affect previously healthy individuals, was only initially suspected in 12%, and had a higher mortality than nonstreptococcal causes. Mean serum creatine phosphokinase (CPK) levels were much higher in patients with necrotizing fasciitis than in those with cellulitis, presumably

reflecting the deeper involvement of musculature, and may be a useful clinical indicator of severity.

The details of 89 patients with necrotizing fasciitis and 225 control individuals (with severe cellulitis or abscess) were used to develop a laboratory risk indicator for necrotizing fasciitis score, which was then validated on a cohort of 140 patients [58]. Predictive laboratory tests proved to be elevated C-reactive protein ( $>150$  mg/L), leukocytosis (especially  $>25 \times 10^9$ /L), low hemoglobin (especially  $<11$  g/dL), hyponatremia  $<135$  mmol/L, creatinine  $>141$   $\mu$ mol/L, and glucose  $>10$  mmol/L; a scoring system of 0–13 was derived, which has positive and negative predictive values of 92% and 96%, respectively, at a cut-off score of 6.

### Comments

Deaths and severe complications are rare among patients with cellulitis. Causes of death are mainly septic shock, multi-organ failure, or related to underlying disease.

There are several factors that contribute to the duration of admission. The duration of admission and the duration of antibiotic therapy are often used as end points of cellulitis treatment. They probably reflect costs, but are not necessarily an accurate surrogate for severity (social issues may contribute to prolonged admissions).

Very few acutely admitted patients will fail to have a full blood count and basic electrolytes tested. Test results such as elevated CPK, rising creatinine, rising liver transaminases, or neutrophilia, may all be associated with severity or with development of streptococcal toxic shock syndrome and/or necrotizing fasciitis. Bacteremia is uncommon in uncomplicated cellulitis, but occurs in about half of patients with necrotizing fasciitis. It appears reasonable to reserve this test for those with recognized local or systemic severity factors. If standard bacteriology cultures are negative, the streptococcal *speB* gene may be detectable in tissue samples using polymerase chain reaction techniques. If present, infection with MRSA appears to predict poor prognosis for patients with cellulitis, and treatment should proceed accordingly for coverage of MRSA.

## What are the long-term complications?

### Evidence summary

Long-term consequences of cellulitis are particularly seen in patients with more severe episodes of infection. Long-term complications include chronic edema of the lower extremity, which has also been identified as a risk factor for the development of cellulitis (reviewed above). A subset of individuals is affected by recurrent cellulitis, often in the same extremity as previously affected. There appears to be a correlation between chronic edema and recurrent cellulitis, representing a vicious cycle of repeated infection and lymphatic distention.

### Prospective studies

We found no prospective studies.

### Retrospective studies

Recurrent episodes were observed in 48 (21%) of 229 patients (79% of cases affected the leg) [12]; 27 of the 229 (12%) had a history of one previous episode, 36 (16%) had had more than one previous episode, and half of those with subsequent episodes had more than one recurrence (most commonly, although not statistically significantly, in those with an underlying cause).

Recurrent episodes were observed in 29% of 143 patients [59]; 13% had two or more further episodes. Risk factors were documented in 26% of those with single episodes, in comparison with 76% of those with recurrent episodes, although only venous insufficiency was statistically significant.

In 70 patients (all with lower-leg sites), morbidity included persistent edema (9%), leg ulceration (3%), and previous or further episodes (28%) [6].

Of 167 admissions (all with lower-leg sites), 77% were for a first-ever episode and 23% for a recurrent episode [16].

Among 459 patients with leg cellulitis (81% of a series of 574 patients), fewer than 30% were admitted due to a first episode of cellulitis; most (about 37% of leg cellulitis admissions during the study period) were for a second episode at the same site, and one-third were due to a recurrent episode at a different site (not stated, but probably the other leg, as the main risk factors in this study affected the legs) [19].

Among 171 patients (retrospective review with questionnaire follow-up at up to 3 years after admission), 47% had a history of recurrent episodes and 46% had chronic edema. There was a strong association between these two factors ( $P = 0.0002$ ) [20]. Chronic edema specific to, or greater in, the previously affected leg was identified by 37%, and 13% had leg ulceration attributed to cellulitis. Both of these complications were less frequent in patients treated with longer courses ( $>28$  days) of penicillin, but the difference did not reach statistical significance. Half of the recurrent episodes of cellulitis had not required hospital admission.

A UK Dermatology Clinical Trials Network (UKDCTN) pilot study to evaluate possible recruitment into trials of cellulitis showed a similar potential for underestimation of recurrent episodes: 40% of patients with cellulitis described previous episodes (multiple in 54% of these), but only 55% had been admitted to hospital during their most recent previous episode [60].

In 209 episodes of leg cellulitis, 35 patients (16.7%) had recurrences within 2 years [61]; possible predictive factors for recurrence were evaluated, and tibial area involvement, prior malignancy, and dermatitis of the ipsilateral limb were all independent risk factors for recurrence on multivariate analysis, with hazard ratios (HRs) of 5.02, 3.87, and 2.9, respectively. If all three were present, the estimated probability of recurrence was 92.8% (95% CI, 51.9–98.9%). Additional factors that had univariate significance included lower-leg edema or venous insufficiency (HR, 3.52 and 3.88, respectively). Interesting factors that did not have even univariate significance included tinea pedis (HR, 1.31) and ipsilateral deep venous thrombosis (HR, 1.66).

A review of 237 patients with lymphedema and recurrent cellulitis demonstrated a direct correlation between the severity of lymphedema and the frequency of recurrence [26].

In a review of 26 patients with lymphatic disorders, decreased lymphatic flow was found to be related to the time since a venous thrombosis, the occurrence and number of episodes of cellulitis/lymphangitis, and use of the saphenous vein for arterial surgery [62].

### Comments

The main long-term complications are persistent edema, a high risk of further episodes, and a less prominent increase in risk of leg ulceration. In addition, there appears to be a significant link between edema and recurrent cellulitis, which is expected, since edema is a well-documented risk factor. A vicious cycle of infection and lymphatic damage may thus be encountered [17,20,62,63].

Any cause of chronic edema, or ongoing portal of entry for streptococci, will predispose to recurrence. It is uncertain why previous malignancy predisposes to recurrences [61]. Lymphatic obstruction caused by tumors is a plausible explanation [24]. It is also uncertain why involvement of the tibial area is linked with a risk of recurrence [61], although involvement of the tibia may have been a surrogate for severity, as the reference comparator was involvement of the foot.

## Does prophylaxis work, and in which patients?

### Evidence summary

No systematic reviews of interventions for prophylaxis of cellulitis have been completed. Randomized controlled trial data available to date point to a protective effect of prophylactic antibiotics. Questions for further investigation remain as to the indications and duration of such therapy. Limited data are available for other prophylactic strategies.

### Antibiotics

#### Prospective studies

An RCT of patients with venous or lymphatic edema who had suffered two or more episodes of cellulitis in the preceding 3 years documented two recurrences in an interventional group of 20 patients treated with prophylactic penicillin ( $n = 15$ ) or erythromycin for penicillin-allergic patients ( $n = 5$ ) in comparison with eight recurrences in 20 control individuals ( $P = 0.06$ ) over a median period of follow-up of 15 months [64].

An RCT of patients with two or more episodes of cellulitis (mainly in the leg) found no recurrences in 16 patients treated with erythromycin, in comparison with 16 control individuals, in whom there were nine recurrences in eight (50%) patients (40 patients entered) [65].

An RCT in patients with recurrent leg cellulitis used IM benzathine penicillin in 24 patients (18 evaluable) in comparison with 34 control individuals (26 evaluable). The active group had no recurrences within a mean of 11.6 months of follow-up, compared with nine (35%) of the controls [66].

In the largest double-blind, randomized, controlled study to date of prophylaxis to prevent further episodes of cellulitis, 123 individuals who had had one or more episodes of cellulitis were randomized to 6 months of low-dose oral prophylactic penicillin V (250 mg twice daily) or placebo twice daily and followed for up to an additional 30 months thereafter (PATCH II) [67]. Patients were excluded from the trial if they had taken antibiotic prophylaxis for the prevention of cellulitis in the preceding 6 months before enrolling. Initial trial design called for the recruitment of 400 study participants, but given difficulties in achieving target recruitment rate, the study was closed after 2 years of recruitment [68]. While not reaching statistical significance, prophylactic treatment with penicillin did show a 47% reduced risk of recurrent cellulitis (HR, 0.53; 95% CI, 0.26–1.07,  $P = 0.08$ ) without differences in adverse events [67].

A second, large randomized trial of cellulitis prophylaxis assessing 12 months of prophylactic penicillin V in patients with at least two previous episodes of recurrent cellulitis (PATCH I) published its findings in May 2013 [70]. Two hundred and seventy-four patients with two or more episodes of cellulitis were randomized to receive either penicillin (250 mg twice daily) or placebo for 12 months, with the primary outcome of interest a first recurrence of cellulitis. During the 1 year of prophylaxis, participants receiving penicillin had a significantly lower recurrence rate (22%) compared

with those receiving placebo (37%; HR, 0.55). However, there was no statistically significant difference between the two groups in the 2 years following the 12-month study period, with similar rates of cellulitis recurrence in the two groups (both 27%) over the next 2 years, suggesting a protective effect limited to periods of active antibiotic prophylaxis.

### Tinea pedis and toe web intertrigo

Tinea pedis or toe web maceration are well-reported risk factors as a portal of entry for infection causing cellulitis [16,21] and have thus been suggested as possible targets for prophylaxis, with some support from individual cases or small groups of cases. However, some larger studies cast some doubt on whether prophylactically treating web space infection is likely to prevent recurrent cellulitis.

In a study primarily investigating the link between edema and recurrent episodes, toe web disease was not well documented by admitting physicians and was only recognized by 15% of patients in a follow-up survey [20]. This prevalence compares with a prevalence of 66% in 167 patients with cellulitis who were examined by dermatologists [16]. Tinea pedis did not have significance as a risk factor for recurrence in a predictive model based on 209 episodes with 35 recurrences [61]. In a study of antibiotic prophylaxis discussed above [65], the 50% recurrence rate in the control group occurred despite treatments for tinea pedis.

### Control of lymphedema

We found no trials.

### Comments

The studies of oral antibiotic prophylaxis suggest that it is beneficial. In a retrospective study of 143 patients in which 19 (13%) had multiple episodes over the following 3 years, prophylaxis was viewed as possibly cost-effective in those with predisposing factors and severe attacks [59].

Despite limited evidence, prophylaxis is used relatively widely. Pavlotsky *et al.* discussed the use of long-term (usually permanent) penicillin in their patients with either recurrent or high-risk primary episodes, and mentioned that 8% of their patients with a recurrence had this whilst on prophylaxis [19]. However, they did not put this into the context of numbers of patients receiving prophylaxis or recurrences after stopping prophylaxis. Among 68 dermatologists who had an interest in research into prophylaxis for cellulitis, 31 used long-term (>1 year) low-dose penicillin for patients with recurrent episodes, and 22 did so if there was a significant risk factor such as lymphedema (UKDCTN, unpublished). The lack of streptococcal resistance to penicillin over many decades [36–38] and its safe use in post-splenectomy patients suggest that this approach is safe for prophylaxis. The CREST guideline suggests that prophylaxis “may be worth trying” in patients who have had two or more episodes of cellulitis at the same site [39]; however, there are reservations about the strength of evidence, which antibiotic and route of administration is best, whether patient-initiated treatment may be more effective than long-term prophylaxis, and whether a prolonged course of treatment after an episode may prevent recurrences.

As documented above, the evidence for prophylaxis of tinea pedis or edema is lacking, albeit logical.

A wider discussion of prophylaxis is provided by Becq-Giraudon [69].



## Key points

- A Cochrane review of interventions for cellulitis completed in 2010 was not able to define the best treatment. This remains an area of ongoing randomized clinical trial study.
- In a normal immunocompetent person, without skin breaks, wounds, or abscess formation, only a few pathogens (usually streptococci or staphylococci) cause cellulitis or other skin or subcutaneous infection [2,40]. Initial therapy should concentrate on these two organisms.
- Community-acquired MRSA represents an increasingly frequent cause of cellulitis, and thought should be given to empiric coverage based on local prevalence patterns.
- Risk factors for lower-leg streptococcal cellulitis have been evaluated in large studies. Combining studies suggests the following risk factors in order of importance: lymphedema, other chronic edema, potential breaks in skin integrity (tinea pedis, dermatitis, wounds), venous insufficiency, and (variably) obesity.
- Adequate-dose flucloxacillin is a suitable initial treatment for presumed streptococcal infection, which accounts for most cases. It also covers staphylococci. Selected cephalosporins are more commonly used for IV home treatment, as they can be administered once daily.
- Risk factors for cellulitis are well documented, but evidence to support secondary prophylaxis is only moderate, and for primary prophylaxis is minimal. Factors to predict or identify complications are well established, but most have greater sensitivity than specificity.
- Numerous local and national guidelines for treating cellulitis have been developed. However, the range of potential organisms, introduction of new antibiotics, differences between body sites in terms of risk factors and likely organism, different clinical scenarios (e.g., presence of lymphedema, wounds), the limited evidence for several scenarios, and the noninferiority methodology of many studies, limit the interpretation of the evidence base in this disorder.
- Further studies are required on the role of systemic antibiotics, physical treatments, and compression bandaging and hosiery for acute management and for prophylaxis.

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# Exanthematic reactions

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## Background

### Definitions

Exanthem, originating from the Greek word for efflorescence and derived from *anthos* or flower (*Stedman's Medical Dictionary*), is defined as any eruptive skin rash that may be associated with fever or other constitutional symptoms [1]. This may be the result of an infectious disease, as an adverse drug reaction, or by interaction between viruses and drugs. Viral infections are frequently associated with the development of exanthems, especially in the pediatric population. These virally induced exanthems are generally nonspecific and often lack characteristic morphologic or distributive features. Some viral exanthems may be associated with enanthems (an eruption of the mucous membrane). Exanthems can include erythematous, vesicular, and petechial types, although most viral exanthems are erythematous papules and macules (Table 47.1). For the purpose of this chapter, an exanthem will not include urticarial, vesicular, blistering, or purpuric lesions. Many of the viral exanthems are associated with low-grade fever, myalgias, headache, rhinorrhea, or gastrointestinal symptoms. Owing to the large number of viral exanthems, the scope of this chapter will be limited to measles, rubella, hand-foot-and-mouth disease, erythema infectiosum, and roseola infantum.

Drug-induced exanthems are often described as maculopapular, scarlatiniform, or morbilliform eruptions. Because of their nonspecific nature, some clinicians frequently use the generic term “drug rash” to depict these cutaneous eruptions. These eruptions manifest as generalized erythematous changes in the skin without evidence of blistering or pustulation. Pruritus is the most frequently associated symptom. In general, these eruptions are observed within the first 10 days of therapy and resolve within 7–14 days. Resolution occurs with a change in color from bright red to a brownish-red, which may be followed by scaling or desquamation. The differential diagnosis in these patients includes a viral exanthem, collagen vascular disease, and bacterial and rickettsial infections. Drug rash with eosinophilia and systemic symptoms (DRESS) – also known as drug hypersensitivity syndrome reaction (HSR) or drug-induced hypersensitivity syndrome (DIHS) – is a complex drug reaction that can affect various organ systems. Fever, skin eruption (usually

an exanthematous eruption), eosinophilia, and internal organ involvement signal this potentially life-threatening syndrome.

### Incidence/prevalence

Infectious agents were identified in 65% of children with acute febrile illness and rash; of these, 72% of cases were caused by viruses and 20% by bacteria [2]. Infection with parvovirus B19 is ubiquitous and occurs worldwide, most commonly in school-aged children [3]. The seroprevalence of parvovirus B19 antibodies increases with direct proportion to age: 2–15% of children 1–5 years of age are immune, 15–60% between 5 and 19 years, and 30–80% of adults [4]. Hand-foot-and-mouth disease is highly contagious, with epidemics occurring every 3 years in the USA. Human herpesvirus (HHV)-6 primarily affects children between the ages of 6 months and 2 years, with the peak age of acquisition between 9 and 21 months. One study concluded that, by 12 months, two-thirds of children have been infected with HHV-6, with peak antibody levels reached at 2–3 years [5]. Furthermore, the seroprevalence for HHV-6 among young adults in the USA reaches almost 100% [6].

Immunization has dramatically reduced the incidence of measles and rubella in developed countries. Routine use of the rubella vaccine has reduced the incidence of rubella in the USA by more than 98%. In addition, routine use of the measles vaccine over the last 30–40 years is estimated to have reduced global measles morbidity and mortality by 74% and 85%, respectively. In the USA, the total number of reported cases of measles during 2001–2003 was 216 [7]. Yet in Africa and Asia, approximately 30 million cases of measles still contribute to almost 900 000 fatalities annually [8].

In the Boston Collaborative Drug Surveillance Program, the prevalence of cutaneous adverse drug reactions in hospitalized patients was 2.2%. Antibiotics were responsible for 7% of detected reactions [9]. Simple exanthematous eruptions are the most common form of drug eruptions, accounting for at least 80% of all skin reactions [10]. In one study of 104 cases, 94% were considered “morbilliform”-type rashes [11].

### Etiology

The classic childhood exanthems include measles, scarlet fever, rubella, erythema infectiosum, exanthema subitum, and chicken

**Table 47.1** Distinctive features of some viral exanthems.

Disease (synonym)	Causative agent	Season of occurrence	Incubation period	Prodrome	Morphology	Duration of rash	Distribution of rash	Associated symptoms
Rubella (German measles, 3-day measles)	RNA virus of Togaviridae family	Spring	14–21 days	Mild fever and respiratory symptoms	Pink macules or papules	1–2 days	Begins on forehead and spreads to trunk and extremities	Lymphadenopathy, splenomegaly
Measles (rubeola)	Paramyxovirus	Winter/spring	10–14 days	High fever, conjunctivitis, cough	Erythematous, discrete, macular and papular rash	3–5 days	Begins on hair line behind ears and over forehead, spreads to trunk	Koplik spots, photophobia
Erythema infectiosum (fifth disease, slapped cheek disease)	Parvovirus B19	Winter/spring	4–14 days	Fever, malaise, headache, coryza	Bright red macular erythema of cheeks, erythematous macular eruption followed by lacy erythema	1–3 weeks	Face, followed by extremities	Aplastic crisis, papular-purpuric syndrome, arthralgia
Roseola infantum (exanthem subitum, sixth disease)	Human herpes virus (HHV)-6 and HHV-7	Spring/fall	9–10 days	High fever for 3–5 days	Rose-pink macules and papules	3–5 days	Trunk, neck, proximal extremities and sometimes face	Mild upper respiratory symptoms, lymphadenopathy, febrile seizures
Hand-foot-and-mouth disease	Enterovirus	Summer/fall	3–6 days	Fever, malaise, abdominal or respiratory symptoms	Vesicular eruption of palms and soles	7–10 days	Hand, foot, mouth	Erosive stomatitis

pox [12]. In addition, there have been more than 50 infectious agents (viral, bacterial, or rickettsial) identified that cause exanthems in children. One study investigated the causes of morbilliform rash in a highly immunized English population. Among 195 children, laboratory confirmation was obtained in 93 cases (48%): parvovirus B19 in 34 (17%), group A streptococcus in 30 (15%), HHV-6 in 11 (6%), enterovirus in nine (5%), adenovirus in seven, (4%), and group C streptococcus in six (3%) [13]. Another study characterized patients, including 108 children and 152 adults, with atypical exanthems; patients with diagnosis of measles, rubella and varicella were excluded. In 201 patients where a causal relationship was established, 47% were due to viruses, 19% due to bacteria, and 32% due to drug. Iatrogenic etiology (i.e., drug-induced) was more prevalent in the winter, whereas infectious etiology, especially from viral infection, was more prevalent in the spring/summer [14].

Measles (rubeola) is a systemic illness caused by a paramyxovirus that is spread by respiratory droplets. Clinical signs and symptoms consist of fever, cough, coryza, conjunctivitis, morbilliform rash, and Koplik spots. Erythematous macules and papules begin at the hairline and behind the ears and spread down the body [15,16].

The enteroviruses, a subgroup of the picornavirus family, cause a variety of different illnesses associated with exanthems. Hand-foot-and-mouth disease, a common and well-recognized entity, is characterized by a vesicular eruption of the palms and soles as well as stomatitis; it is most commonly associated with coxsackievirus A16 or enterovirus 71 [17]. After an incubation of 3–6 days, low-grade fever, malaise, and abdominal or respiratory symptoms are present. Cutaneous lesions appear as pink to red macules or papules in a characteristic linear arrangement.

Roseola infantum (exanthem subitum, sixth disease) is caused by primary infection with HHV-6 and HHV-7. High fever in an otherwise well-appearing child and a rash with defervescence are

classic findings. The exanthem consists of pink macules and papules that spread from the neck down to the trunk and proximal extremities [4]. Erythema infectiosum (fifth disease) is caused by parvovirus B19. After a 3–18-day incubation period, mild symptoms such as fever, malaise and sore throat develop in 20–60% of cases 2 days before the rash. The exanthem has a characteristic “slapped cheek” appearance; erythematous, edematous, confluent plaques appear symmetrically on both cheeks [4]. Manifestations significantly associated with acute parvovirus B19 infection in immunocompetent children were exanthema, anemia, and leukopenia [18]. In healthy adults, parvovirus B19 usually causes a self-limiting febrile illness, accompanied by other features such as polyarthralgia and facial erythema. Clinically significant arthropathy that may persist for weeks to months is found in 50% of adult patients infected with parvovirus B19 [3,19]. Infections in immunocompromised hosts can lead to chronic infection, most often manifested as chronic anemia [4].

Rubella (German measles), caused by the rubella virus, is usually a mild disease consisting of low-grade fever, generalized erythematous macules and papules, which last 3 days, and generalized lymphadenopathy. In adolescents and adults, but not in children, there is a prodromal period with fever, malaise, sore throat, nausea, and anorexia. An enanthem, called Forchheimer spots, consists of petechiae on the hard palate, and may be present in some patients.

Exanthematous eruptions can be caused by many drugs, including the beta-lactams, sulfonamides, nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine), and antiepileptic medications [20]. The incidence of delayed cutaneous eruptions associated with ampicillin or amoxicillin is 9.5% [21]. Exanthematous eruptions can appear 2–3 days after the drug is started, although they most frequently occur after 8–10 days of therapy. Gemifloxacin, a fluoroquinolone, is associated with a mild to moderate self-limiting

maculopapular rash, especially when used beyond 7 days. When used for 5 days for community-acquired respiratory tract infections, the rash rate is typically less than 1.5%, a rate similar to that with other fluoroquinolones [22]. Since most drugs can cause an exanthematous eruption, it is important to obtain a detailed medication history, including over-the-counter preparations and herbal and naturopathic remedies in patients with a history of an adverse drug reaction. New drugs started within the preceding 6 weeks are potential causative agents for most cutaneous eruptions, as are drugs that have been used intermittently. Approximately 10–20% of all exanthematous eruptions in children are considered to be drug induced, whereas 50–70% of exanthematous eruptions in adults are triggered by drugs.

Drugs that have been reported to cause DRESS include the aromatic anticonvulsants (i.e., phenytoin, phenobarbital, oxcarbazepine, and carbamazepine), lamotrigine, sulfonamide antibiotics, dapsone, nitrofurantoin, nevirapine, minocycline, and allopurinol. In a review of 172 published cases, the most frequently associated drug was carbamazepine, followed by allopurinol, lamotrigine, phenobarbital, and sulfasalazine [23]. Although this reaction has been estimated to occur in between 1 in 1000 and 1 in 10000 anticonvulsant and sulfonamide antibiotic exposures, its true incidence is unknown because of variable presentation and inaccurate reporting.

### Prognosis

Many of the viral exanthems are self-limiting conditions. However, some of the viral illnesses can result in significant morbidity and mortality. In the USA, the mortality rate for *measles* is 0.3%, but in developing countries it can reach 1–10%. Complications include pneumonia, croup, diarrhea, acute encephalitis, brain damage, and death from respiratory and neurologic complications. Measles is one of the leading causes of death among young children, mostly in children under 5 years of age [24]. The most frequent complication of *roseola* is febrile seizures. Among 902 children under 3 years of age with primary HHV-6 infection and fever, 149 (16.5%) had a seizure [25]. Approximately 5% of adult patients and 10% of children undergoing chemotherapy for hematological malignancies are persistently infected with the parvovirus B19 virus (*erythema infectiosum*), resulting in severe and even lethal cytopenias [19]. Arthralgia and arthritis are the most common complications following *rubella*, occurring in up to 70% of postpubertal females [26]. Enterovirus 71-mediated *hand-foot-mouth disease* may be accompanied by central nervous system and pulmonary complications [27].

Many of the viral illnesses acquired during pregnancy may result in adverse outcomes for the fetus. When rubella occurs during the first trimester of pregnancy, the infection can result in approximately 50% of fetuses with manifestations of congenital rubella syndrome, which includes congenital heart defects, cataracts, microphthalmia, deafness, microcephaly, and hydrocephalus [28]. Similarly, although rare, hand-foot-and-mouth disease acquired during first trimester of pregnancy may result in spontaneous abortion. Erythema infectiosum acquired during fetal development may be complicated by fetal hydrops secondary to infection of erythroid precursors, hemolysis, severe anemia, tissue anoxia, and high-output failure. Fetal loss was 6.5% in a series of 334 cases, with 0.6% with nonfatal hydrops fetalis [29].

Simple exanthematous eruptions due to medications generally resolve spontaneously without complications or sequelae within 7–14 days. However, DRESS reactions may, in rare cases, result in significant morbidity and even mortality.

### Diagnostic tests

Many viral infections, including hand-foot-and-mouth disease and erythema infectiosum, are straightforward clinical diagnoses. In addition to the clinical presentation of the exanthem and any enanthem, diagnosis is based on the patient's history (e.g., exposure to other infected individuals) and other distinguishing features of the viral infection, such as predilection for certain seasons. However, confirmation of various viral infections can be accomplished via laboratory tests. Viral culture or polymerase chain reaction (PCR)-based tests can be used for diagnosis of enteroviral infection. Rubella can be diagnosed by detection of anti-rubella IgM antibodies, or a fourfold increase in serum IgG levels. Tests for detection of B19 DNA are required in immunocompromised patients who are unable to mount an adequate humoral response. Methods that detect viral particles or viral DNA are amplified by PCR [4]. Detection of serum anti-B19 IgM antibody can also be used when diagnostic confirmation of B19 infection is needed [19]. However, caution is suggested when interpreting serology in immunodeficient individuals and pregnant women, as they may not necessarily be able to mount an antibody response.

In general, skin biopsies are not indicated for diagnosis of viral exanthem, owing to the nonspecific findings. In addition, a biopsy of drug-induced exanthematous eruptions is generally not necessary, as nonspecific changes are usually present that consist of a mild perivascular lymphocytic infiltrate and a few necrotic keratinocytes within the epidermis.

Some exanthematous eruptions can be identified through patch or delayed-reading intradermal skin tests. Immediate prick skin testing for drug-induced exanthematous eruptions is not helpful in most cases, as skin testing is usually reserved for the diagnosis of IgE-mediated reactions. However, skin testing has been used in the confirmation of delayed ampicillin and amoxicillin exanthematous eruptions [30]. Patch testing, using the drug in a suitable concentration, can be used to confirm various delayed type IV reactions, including contact dermatitis and delayed exanthematous eruptions [31]. The overall sensitivity of patch testing is estimated to be 30–60%, which suggests that a negative patch test does not exclude a drug-induced reaction [32]. One study concluded that patch testing was found to be a useful screening tool if the reaction was exanthematous and if antimicrobial, cardiovascular, or antiepileptic drugs were suspected. A positive patch test to one or more drugs was observed in 89 of 826 patients (10.8%), most often to beta-lactams, clindamycin, and trimethoprim [33].

Diagnostic or confirmatory tests are not readily available for patients with the HSR. An in-vitro test employing a mouse hepatic microsomal system is used for research purposes to characterize patients who develop this serious reaction [34]. Because of the severity of the reaction, oral rechallenges and desensitizations are not recommended, as reexposure to the offending agent may cause development of symptoms within 1 day.

Differential diagnosis for drug-induced exanthems includes viral exanthems (e.g., enteroviruses, HHV-6, parvovirus B19, Epstein-Barr virus (EBV)) and other illnesses such as bacterial and rickettsial diseases, graft-versus-host disease and Kawasaki's syndrome [35,36]. It is often difficult to discriminate between a drug-induced morbilliform eruption and a viral exanthem, although the polymorphic nature of the cutaneous eruption favors a drug eruption. Other features that may help distinguish between a drug-induced and a viral eruption include onset of reaction in relationship to drug, history of previous reaction to a medication, exposure to infected individuals with a similar viral infection, and



characteristic appearance of the rash (e.g., “slapped cheek” for erythema infectiosum).

### Aims of treatment

For most viral and drug-induced exanthems, the aims of treatment are supportive and include reduction of fever, relief of pruritus, and/or management of arthralgias. In immunocompromised patients, the aims of treatment include symptomatic management as well as prevention of complications such as pneumonia, encephalitis, and hepatitis. The aims of treatment in patients with DRESS include symptomatic management and prevention of serious complications such as hepatitis, nephritis, or pneumonitis. Desensitization regimens are generally not recommended for non-IgE-mediated reactions (such as exanthematous eruptions, including DRESS); rather, desensitization protocols are used for IgE-mediated reactions such as anaphylaxis [37].

### Relevant outcomes

For viral and drug-induced exanthems:

- fever;
- extent of exanthem;
- arthralgias and other systemic features, such as malaise, nausea/vomiting, diarrhea;
- resolution of symptoms;
- death.

For drug-induced exanthems:

- onset of symptoms, in temporal relationship to initiation of drug therapy;
- internal organ involvement;
- death.

### Methods

The databases of the Cochrane Library to 2012 and Medline between 1968 and August 2012 were searched for the following terms:

- measles, rubella, roseola, exanthema subitum, fifth disease, parvovirus B19, human, erythema infectiosum, hand-foot-and-mouth disease;
- exanthema, drug eruptions, drug hypersensitivity, skin diseases viral, viral exanthem, drug exanthems, skin diseases.

Subheadings used with the search terms, when appropriate, included “chemically induced,” “epidemiology,” “drug therapy,” “diagnosis,” and “treatment.” Other search terms used in combination with the above terms included “pregnancy” (e.g., rubella and pregnancy), “skin tests” (e.g., skin tests and drug eruptions), “ampicillin,” and “infectious mononucleosis.”

## Questions

### What is the pathogenesis for drug-induced exanthems?

Constitutional factors influencing the risk of cutaneous eruption include pharmacogenetic variation in drug-metabolizing enzymes and human leukocyte antigen (HLA) associations. HLA factors may influence the risk of reactions to nevirapine, abacavir, carbamazepine, and allopurinol [38–41]. Allopurinol-induced adverse reactions, including DRESS, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been strongly associated with a genetic predisposition among Han Chinese; the HLA-B\*5801 allele was found to be an important genetic risk factor [38]. A meta-

analysis found a strong and significant association between HLA-B\*5801 and allopurinol-induced SJS/TEN (using matched control: odds ratio [OR], 96.60; 95% confidence interval [CI], 24.49–381;  $P < 0.001$ ) [42]. The HLA-B\*1502 allele is strongly associated in subjects of Chinese/Asian ethnicity with carbamazepine-induced SJS and TEN, but not with nonblistering eruptions such as exanthematous eruptions or DRESS [41,43]. No correlation between HLA-B\*1502 and carbamazepine-induced SJS/TEN has been found in Caucasians [44]. However, the HLA-A\*3101 allele was associated with carbamazepine-induced hypersensitivity reactions among subjects of northern European ancestry [45]. In addition, the HLA-A\*3101 allele had a 60.7% sensitivity and 87.5% specificity when this allele was applied as a risk predictor for carbamazepine-induced cutaneous adverse drug reactions (including SJS/TEN) in the Japanese population [45]. These data suggest that genetic susceptibility is both phenotype and drug specific [46].

Nevirapine has been associated with HSR involving various combinations of fever, hepatitis, or rash. Studies have suggested that HLA-DRB1\*0101 and the CD4 status of a patient may determine susceptibility to nevirapine hypersensitivity [39]. Abacavir is also associated with a potentially life-threatening adverse reaction in approximately 8% of patients initiated on this drug. Studies have shown that there is a strong predictive association between abacavir HSR and HLA-B\*5701 [47].

Many drugs associated with severe idiosyncratic drug reactions are metabolized by the body to form reactive, or toxic, drug products [48]. These reactive products comprise only a small proportion of a drug's metabolites and are usually rapidly detoxified. However, patients with DRESS and TEN/SJS, resulting from treatment with sulfonamide antibiotics and the aromatic anticonvulsants, show increased sensitivity in in-vitro assessments to the oxidative, reactive drug metabolites of these drugs in comparison with control individuals [49].

Acquired factors also alter an individual's risk of drug eruption. Active viral infection and concurrent medications have been shown to alter the frequency of drug-associated eruptions. For example, valproic acid increases the risk of severe cutaneous adverse reactions to lamotrigine, another anticonvulsant [50]. The basis of these interactions and reactions is unknown, but may represent a mixture of factors, including alteration in drug metabolism, drug detoxification, antioxidant defenses, and immune reactivity.

The course and outcome of drug-induced disease are also influenced by host factors. Older age may delay the onset of drug eruptions and has been associated with a higher mortality rate in some severe reactions. A higher mortality rate is also observed in patients with severe reactions with underlying malignancy [51].

Although the underlying pathogenesis for many drug eruptions remains unknown, certain studies have shown that drug-specific T cells play a major role in exanthematous, bullous, and pustular drug reactions [52]. Immunohistochemical studies have shown that the cell infiltrate in drug-induced maculopapular exanthems is mainly composed of CD3<sup>+</sup> T cells (40–70%), with a predominance of CD4<sup>+</sup> cells [53]. Cytotoxic T cells (more CD4 cells than CD8 cells) contribute to the characteristic features of interface dermatitis, such as vacuolar alteration and keratinocyte death [54].

### What are the features of a reaction known as drug rash with eosinophilia and systemic symptoms?

A widespread rash, often an exanthematous eruption, in conjunction with fever, internal organ involvement (e.g., liver, kidney,

central nervous system), and eosinophilia signifies a more serious reaction, known as DRESS. The condition is also known as HSR and as DIHS. This syndrome has been well described for a number of drugs, including anticonvulsants, sulfonamide antibiotics, dapsone, minocycline, and allopurinol. DRESS occurs most frequently on first exposure to the drug, with initial symptoms starting 2–6 weeks after exposure to the drug. In patients with a history of DRESS, reexposure to the offending agent may cause development of symptoms within 1 day. DRESS is not related to dose or serum concentration of the drug.

A mild to high fever ranging from 38 to 40°C and malaise, which can be accompanied by pharyngitis and cervical lymphadenopathy, are the presenting symptoms in most patients. Atypical lymphocytosis with a subsequent prominent eosinophilia may occur during the initial phases of the reaction in many patients. A generalized exanthem occurs in approximately 85% of patients, usually simultaneously with the appearance of the fever or shortly after. Skin manifestations can range from an exanthematous eruption to more serious eruptions, such as exfoliative dermatitis [55]. Conjunctivitis and angioedema of the face may also be present in some patients, especially patients with anticonvulsant-induced HSR. Liver abnormalities, presenting as elevated transaminases, alkaline phosphatase, prothrombin time, and bilirubin, are present in approximately 50% of patients; in some patients, development of severe hepatitis with jaundice may occur. Other organs, such as the kidney (interstitial nephritis, vasculitis), central nervous system (encephalitis, aseptic meningitis), or lungs (interstitial pneumonitis, respiratory distress syndrome, vasculitis) may less commonly be involved. In a report of 27 patients with DRESS, hepatic and hematological involvements were the two most common systemic complications, occurring in 96% and 85%, respectively [56]. Although resolution occurs in most patients upon discontinuation of the offending drug, some patients have flare-ups with fever, skin eruption, or hepatitis that may occur several weeks after drug withdrawal [57]. A small subgroup of patients may become hypothyroid as part of an autoimmune thyroiditis within 2 months of initiation of symptoms [58]. This is characterized by a low thyroxine level, an elevated level of thyroid-stimulating hormone, and thyroid autoantibodies, including antimicrosomal antibodies.

Diagnostic criteria have been developed for DRESS in hospitalized patients: rash plus three of four systemic features (fever, lymphadenopathy, internal organ involvement, hematological abnormalities) [59]. Diagnostic criteria have also been developed by a Japanese consensus group and include maculopapular rash, prolonged clinical symptoms 2 weeks after discontinuation of the causative drug, fever, liver abnormalities, leukocyte abnormalities, lymphadenopathy, and HHV-6 reactivation [57].

Cross-reactions have been reported with the aromatic anticonvulsants. In one study, 75% of a series of patients with anticonvulsant hypersensitivity syndrome to one aromatic anticonvulsant showed in-vitro cross-reactivity to the other two [60]. In addition, in-vitro testing showed that there is a familial occurrence of hypersensitivity to anticonvulsants. Because siblings and other first-degree relatives are at increased risk (perhaps as high as one in four) of developing a similar adverse reaction, counseling of family members is essential. Although lamotrigine is not an aromatic anticonvulsant, there have been several reports documenting a hypersensitivity syndrome associated with its use [61].

Sulfonamide antibiotics are also metabolized to toxic metabolites – namely, hydroxylamines and nitroso compounds [62]. In most people, detoxification of the metabolite occurs. However, DRESS

may occur in patients who are unable to detoxify this metabolite. Other aromatic amines, such as procainamide, dapsone, and acebutolol, are also metabolized to chemically reactive compounds. We recommend that patients who develop symptoms compatible with a sulfonamide hypersensitivity syndrome reaction avoid these aromatic amines, because the potential exists for cross-reactivity [63]. However, cross-reactivity should not necessarily occur between sulfonamide antibiotics and drugs that are not aromatic amines (e.g., sulfonyleureas, thiazide diuretics, furosemide, and acetazolamide) [64].

The differential diagnosis of DRESS includes other cutaneous drug reactions, acute viral infections, lymphoma, and idiopathic hypereosinophilic syndrome. After DRESS has been diagnosed, there are a minimum number of laboratory tests that help to evaluate internal organ involvement, which may be asymptomatic. Liver transaminases, complete blood count, and urinalysis and serum creatinine should be performed at the initial evaluation. In addition, the clinician should be guided by the presence of symptoms, which may suggest specific internal organ involvement (e.g., respiratory symptoms). Thyroid function tests should be measured and repeated after 2–3 months. A skin biopsy may be helpful if the patient has a blistering or a pustular eruption. Unfortunately, readily available diagnostic or confirmatory tests to establish drug causation are not readily available. An in-vitro test using a mouse hepatic microsomal system is used for research purposes to evaluate patients who develop DRESS [34]. Oral rechallenge or desensitization is not recommended, owing to the severity of the DRESS reactions.

There are no controlled trials of treatment in DRESS. Although the role of systemic corticosteroid therapy is controversial, most clinicians would elect to start prednisone at a dosage of 1–2 mg/kg per day if symptoms are severe, although dosages as low as 0.5 mg/kg per day have also been recommended [65]. There are cases of patients who have been treated with ciclosporin [66] or intravenous immunoglobulin (IVIg) [67]. Antihistamines or topical corticosteroids can also be used to alleviate symptoms. Because the risk of DRESS is substantially increased in first-degree relatives of patients who have had DRESS reactions, counseling of family members is a crucial part of the assessment of this syndrome.

### What role do viruses play in the development of drug eruptions?

Various risk factors may contribute to the development of an adverse drug reaction, including genetic predisposition, drug–drug interactions, and viral infections. Viral infections may create biological alterations in the immune system that enhance the risk of adverse drug reactions.

EBV is the cause of most acute infectious mononucleosis syndromes. Patients primarily present with malaise, fever, pharyngitis, and lymphadenopathy. In patients who have infectious mononucleosis, the risk of developing an exanthematous eruption while being treated with an aminopenicillin (e.g., ampicillin) increases from 3–7% to 60–100% [68]. The rash is extensive, maculopapular, pruritic, and usually accompanied by fever. Although the mechanism of the reaction has not been clarified, it does not appear to be IgE-mediated [69]. In fact, the patient with infectious mononucleosis who develops a delayed rash while on an aminopenicillin is not at risk from developing the same reaction when reexposed to the aminopenicillin or any penicillin without a concurrent EBV infection.

Approximately 50–60% of patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) who are exposed to sulfonamide antibiotics for *Pneumocystis carinii* infection develop adverse reactions such as fever, rash, neutropenia, and hepatitis [70]. In addition to the presence of HIV, the increased prevalence of slow acetylation and altered activity of oxidative metabolic pathways in AIDS patients with acute illnesses may partly explain the increased incidence of adverse reactions in these patients [71,72].

Reactivation of latent viral infection with HHV-6 also appears common in DRESS and may be partly responsible for some of the clinical features and/or course of the disease [57,73–76]. These viral reactivations have been reported in association with recurrence of symptoms more than 2 weeks after the drug was discontinued [76]. Viral infections may act as, or generate the production of, danger signals leading to damaging immune responses to drugs, rather than immune tolerance [77]. Other viruses, including HHV-7, EBV, and cytomegalovirus, can be reactivated during the course of DRESS [78].

### What treatment regimens have been used in patients infected with viral exanthems?

Most viral exanthems are self-limiting conditions that only require symptomatic treatment. This includes the use of antipyretics (e.g., acetaminophen, ibuprofen) and analgesics (i.e., nonsteroidal anti-inflammatory drugs) in cases of arthralgias. For patients with pruritus, relief can be obtained with antihistamines, topical antipruritic lotions (e.g., calamine), or topical corticosteroids.

### Parvovirus B19

Treatment is usually limited to nonsteroidal anti-inflammatory drugs for management of joint complaints [12]. IVIg has been used in the treatment of patients with chronic or persistent infections due to parvovirus B19; this includes children with immunodeficiency syndromes, chemotherapy-induced suppression, transplant patients, and patients with HIV/AIDS [4]. A persistent parvovirus B19 infection responds to a 5-day or 10-day course of IVIg at a dose of 0.4 g/kg of body weight, with a prompt decline in serum viral DNA, accompanied by reticulocytosis and increased hemoglobin levels [3]. IVIg has also been administered at 1 g/kg for 3 days [18]. Intrauterine red-cell transfusions have been used for the treatment of intrauterine infections with fetal hydrops and anemia, although hydrops fetalis may resolve spontaneously [79].

### Human herpesvirus 6

There are no medications available that are specific for HHV-6. Ganciclovir and foscarnet have been used for serious HHV-6 disease in immunocompromised and transplant patients, but there are no randomized trials. One report described two patients treated early with foscarnet for HHV-6 encephalitis after bone-marrow transplantation. Both patients improved on therapy [80,81]. Antiviral prophylaxis with ganciclovir prevented HHV-6 reactivation in six bone-marrow transplant recipients [82].

### Measles

Vitamin A deficiency is a recognized risk factor for severe measles. The protective effect of vitamin A on measles mortality was shown more than 70 years ago [83]. Measles can decrease serum concentrations of vitamin A in well-nourished children to levels less than those observed in malnourished children without measles. Vitamin A deficiency depresses the immune function and can destroy epi-

thelial tissue; therefore, vitamin A may prevent the complications of measles infection by stimulating the body's impaired immune reaction, by a direct activating effect on helper T cells and by boosting immunoglobulin production [84].

In 1997, the World Health Organization and United Nations Children's Fund (UNICEF) recommended that 200 000 IU of vitamin A should be given twice to children with measles over the age of 1 year in populations in which vitamin A deficiency may be present. If there is clinical evidence or great risk for vitamin A deficiency, the dose is repeated after 4 weeks [85]. The American Academy of Pediatrics suggests that vitamin A be administered to patients aged 2 years or less who are hospitalized with measles and its complications [86]. It should also be administered to patients who are older than 6 months but have an immunodeficiency, ophthalmological evidence of vitamin A deficiency, impaired intestinal absorption, moderate to severe malnutrition, or recent immigration from areas where a high mortality rate from measles has been observed.

There have been several meta-analyses that have evaluated whether vitamin A is beneficial in preventing mortality, pneumonia, and other secondary infections in children with measles [83,85]. In the Cochrane review, eight trials met the inclusion criteria. Overall, there was no significant reduction in the risk of mortality in the vitamin A group when the studies were pooled using the random-effects model (relative risk [RR], 0.70; 95% CI, 0.42–1.15). However, two doses of vitamin A 200 000 IU on consecutive days were associated with a reduction in the risk of mortality in children under the age of 2 years (RR, 0.18; 95% CI, 0.03–0.61) and a reduction in the risk of pneumonia-specific mortality (RR, 0.33; 95% CI, 0.08–0.92). There was no evidence that vitamin A in a single dose reduced the risk of mortality. There was a decrease in the incidence of croup, but no significant reduction in the incidence of pneumonia or diarrhea with two doses [83]. Another meta-analysis evaluated whether vitamin A supplementation in children prevents blindness, although no studies were found that examined the efficacy of vitamin A in preventing blindness [87].

In spite of the possible role of oxidative stress in conditions such as viral infections, vitamins E and C have not been shown to provide any benefit in the course of the illness in children with measles and pneumonia [88]. Studies evaluating the efficacy and safety of Chinese medicinal herbs were systematically reviewed in a Cochrane review; unfortunately, none of the trials concealed the allocation or blinding method, and therefore no analyses were performed [89]. There is no specific antiviral therapy for measles, although ribavirin has been used in patients with measles with severe manifestations [90].

A meta-analysis was done to assess the effects of antibiotics given to children with measles to prevent complications and reduce pneumonia. Seven trials that included 1263 children were included. Although the data showed that the incidence of pneumonia was lower in the treatment group compared with the control group, the difference was not statistically significant. However, eliminating a trial that was conducted in 1942, a statistically significant reduction in the incidence of pneumonia was observed in children receiving antibiotics (OR, 0.26; 95% CI, 0.12–0.60) [91].

### Hand-foot-and-mouth disease

Acyclovir has been studied in the treatment of hand-foot-and-mouth disease in a preliminary report. Symptomatic relief, defer-escence, and significant involution of lesions were seen within 12 h of starting acyclovir (200–300 mg five times daily for 5 days) [92].



In another report, an immunocompromised 27-year-old man with a prolonged course of hand-foot-and-mouth disease was started on oral acyclovir 200 mg five times daily, with subsequent resolution of all lesions within 5 days [93].

### Key points

- Most drug-induced exanthems manifest as generalized erythematous changes in the skin without evidence of blistering or pustulation. Pruritus is the most frequently associated symptom. These eruptions generally occur within the first 10 days of therapy and resolve within 7–14 days after discontinuation of the medication.
- Many of the viral illnesses acquired during pregnancy may result in adverse outcomes for the fetus. For example, when rubella occurs during the first trimester of pregnancy, the infection can result in approximately 50% of fetuses with manifestations of congenital rubella syndrome.
- Diagnosis of viral infections includes the clinical presentation of the exanthem and enanthem, and the patient's history (e.g., exposure to other infected individuals and distinguishing features of the viral infection). Laboratory tests can be done for confirmation, if necessary.
- Diagnosis of drug-induced exanthematous eruptions is based on the clinical history. The use of confirmatory tests, such as patch or delayed reading of intradermal skin tests, has not been well defined.
- The aims of treatment for most viral and drug-induced exanthems are supportive and include reduction of fever, relief of pruritus, and/or management of arthralgias.
- Factors that may influence the risk of a cutaneous eruption include pharmacogenetic variation in drug-metabolizing enzymes and HLA associations, acquired factors (e.g., active viral infection and concurrent medications), host factors (e.g., age, underlying malignancy), and drug-specific T cells.
- DRESS is comprised of a cutaneous eruption (usually exanthematous), fever, eosinophilia, and internal organ involvement. This reaction usually occurs on first exposure to the drug, with initial symptoms starting 2–6 weeks after exposure to the drug. This reaction is most commonly associated with the aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), sulfonamide antibiotics, allopurinol, dapsone, and minocycline.

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# Herpes simplex

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## Background

### Definition

Herpes simplex virus (HSV) is a human pathogenic DNA virus that causes a variety of disease manifestations, ranging from localized skin and mucous membrane lesions to severe disseminated infections (such as neonatal herpes simplex, eczema herpeticum, and herpetic meningoencephalitis). The infection is frequently acquired in an occult manner or it may present as primary herpetic gingivostomatitis, which can include oral as well as extraoral lesions, swollen and bleeding gums, pain, fever, irritability, malaise, headache, and upper respiratory tract infection [1]. Following the primary infection, the virus resides in the sensory ganglia in a latent form. Upon reactivation, symptomatic recurrent lesions or asymptomatic virus shedding occurs.

In recurrent manifestations, grouped vesicles are predominantly located at the lips and nostrils, in the mouth and face, and on the genitals. They may rupture and ulcerate. Lesions are accompanied by pain and/or itching, and in genital lesions also with dysuria and malaise.

### Etiology

HSV infections are transmitted by two virus species, HSV-1 and HSV-2, belonging to the group of double-stranded DNA-type viruses (Herpesviridae family, subfamily Alphaherpesvirinae, genus *Simplexvirus*) (Figures 48.1 and 48.2). HSV-1 is still most frequently transmitted by saliva and HSV-2 by genital transmission [2–4], although these findings are no longer reliable in individual cases. Infection is contracted through direct skin contact (not necessarily in the genital area) with an infected person, and less frequently by indirect contact. Transmission can occur not only during an active symptomatic HSV manifestation, but also from virus shedding from the skin in the absence of symptoms [5,6]. The peak viral DNA load has been reported to occur after 48 h, with no virus detected beyond 96 h after the onset of symptoms [7]. In general, symptoms appear 3–6 days after contact with the virus, but may not appear for up to a month or more after infection.

### Incidence/prevalence

HSV-1 infection frequently occurs during childhood, and over 90% of adolescents have specific antibodies in their sera indicating a previous primary (maybe occult) infection. Only 5–10% of patients initially infected with the HSV develop clinical lesions of a primary herpetic gingivostomatitis [1]. The lifetime prevalence of recurrent herpes labialis is 20–40% [8].

For HSV-2, there is an increasing prevalence of about 20% from the age of puberty onward [2,4]. Symptomatic recurrent flares occur in 20–50% of patients who have anti-HSV antibodies. Following a symptomatic first episode of HSV-2 genital infection a median recurrences rate is of four recurrences during the first year. The rate of recurrence usually decreases over time, but in about one-quarter of the patients it increases [9].

### Prognosis

Active localized manifestations heal spontaneously within 2–6 weeks without scarring, unless bacterial superinfection has occurred. However, herpes simplex establishes a latent infection in cells of the nervous system by incorporation of double-stranded DNA into the cell nucleus, which can be reactivated by certain trigger factors (e.g., febrile infections, trauma, menstruation, stress, intense ultraviolet exposure). Disseminated systemic disease may be fatal.

### Diagnostic tests

In most cases, the diagnosis is based on the characteristic clinical appearance of lesions. In uncertain cases, diagnostic tests and proof of virus can be necessary. HSV can be grown in virus culture from vesicles, swabs from skin and mucous membranes, tissue biopsies, and cerebrospinal fluid (during the first 2 days of disease manifestation). Whereas these tests take several days to complete, a Tzanck smear from the base of a fresh blister takes only minutes. However, the Tzanck preparation only shows signs of infection (giant cells with multiple nuclei) in 50–79% of patients with a herpes infection, and a negative Tzanck preparation may have to be confirmed by a herpes culture. Detection of HSV antigen (by direct



**Figure 48.1** HSV-1 infection most frequently presents orally and at the lips. Recalcitrant recurrences of labial herpes (HSV-1) may be triggered by a variety of factors. The painful and visible lesions often cause severe discomfort in the patient seeking for medical advice.



**Figure 48.2** HSV-2 infection presents most frequently as genital herpes. Lesions are accompanied by pain and/or itching, and sometimes dysuria and malaise. Recalcitrant recurrences may severely hamper the quality of life.

immunofluorescence) or HSV DNA (by polymerase chain reaction) are further diagnostic tests for valid diagnosis of HSV infection. In individuals with a primary HSV infection, specific IgM antibodies can be detected after 10 days (e.g., using a Western blot assay), followed by a subsequent increase in IgG antibodies. Reactivation cannot be adequately confirmed serologically.

### Aims of treatment

Episodes of active disease are self-limiting in the immunocompetent adult. However, many patients with primary and recurrent

genital and extragenital herpes simplex may seek treatment because of discomfort associated with the lesions during active disease, the virus shedding, and the duration of the condition.

### Relevant outcomes

Clinical cure of active lesions is the clinically most relevant outcome. Treatment success is defined as shortening of the duration of pain, active lesions, and virus shedding. Secondary outcomes include time to recurrence and reactivation of latent infection.

### Methods of search

The Cochrane Library for Systematic Reviews (January 2013), the Cochrane Controlled Trials Register (January 2013) and Medline (1966–January 2013) were searched for systematic reviews of randomized controlled trials (RCTs) and high-quality individual RCTs of all interventions for primary and secondary herpes simplex infections in immunocompetent adults.

If no systematic reviews or RCTs were found, this is stated and the next best evidence (e.g., large nonrandomized controlled studies, cohort studies, or large case series) is discussed with suitable warnings regarding potential bias.

### Questions

#### Which treatment in primary manifestation of an oral/labial herpes simplex is beneficial with regard to total lesion clearance in the immunocompetent adult?

##### Efficacy

No systematic review or individual RCTs were found on therapeutic interventions with *topical* antiviral agents versus placebo/no treatment at first onset of a primary oral manifestation of HSV in immunocompetent adults.

A Cochrane systematic review (CSR) on *systemic* aciclovir in the treatment of primary herpetic gingivostomatitis in children and young adults (under the age of 25) has been published [1].

Only two RCTs, one with 72 participants and the other with 20 participants, were included in this review. The second study failed to report several methodological items and was inconsistent in its reporting of the outcomes measurement [1].

The first trial, with a moderate risk of bias, showed better results in the aciclovir group (15 mg/kg five times per day for 7 days started within 3 days after onset of herpetic gingivostomatitis) compared with the placebo group in children <6 years of age: in reducing the number of individuals with oral lesions (risk ratio [RR], 0.10; 95% confidence interval [CI], 0.02–0.38), new extraoral lesions (RR, 0.04; 95% CI, 0.00–0.65), difficulty in eating (RR, 0.14; 95% CI, 0.03–0.58), and drinking difficulties (RR, 0.11; 95% CI, 0.01–0.83) after 8 days of treatment. The time to healing was significantly shorter in the children receiving aciclovir (median: 4 days; range: 2–12 days) than in those receiving placebo (median: 10 days; range: 3–15 days) [1].

The second double-blind RCT in 20 children with a mean age of 2 years with a primary manifestation of herpetic stomatitis/gingivitis of less than 4 days' duration compared oral aciclovir (200 mg five times per day) with placebo. Active treatment reduced the mean duration of pain (4.3 days with aciclovir vs 5.0 days with placebo;  $P = 0.05$ ), however, details of pain assessment in this age group are unavailable.



## Drawbacks

No significant adverse effects occurred in either group of treated children [1].

## Comments

The data are derived from two trials conducted in children. No RCTs on interventions for a primary manifestation of an oral/labial herpes simplex infection in the immunocompetent adults were found. There is a need for trials to be conducted in other age groups.

## Implications for clinical practice

On the basis of data obtained in affected children, oral antiviral agents (aciclovir) are likely to be beneficial in the first onset of oral/labial herpes simplex. Topical antiviral agents are of unknown effectiveness for primary manifestations of oral/labial herpes simplex in the immunocompetent adult.

## Which therapeutic interventions are beneficial for preventing recurrences of labial herpes simplex in immunocompetent adults?

### Efficacy

No systematic review is currently available. A protocol for a CSR on any systemic, topical, or physical intervention used for the prevention of recurrent labial herpes simplex (HSL) in immunocompetent individuals has been registered (dated 2012) [10].

To date, six RCTs were found on the suppression of oral recurrences in immunocompetent adults by prophylactic intake of oral antiviral agents [11–15]. Their results are discordant.

The first RCT observed a reduction in the frequency and duration of labial recurrences in skiers ( $n = 147$ ) with a history of ultraviolet-precipitated HSL using prophylactic oral aciclovir (400 mg twice daily, beginning 12 h *before* ultraviolet exposure) in comparison with placebo ( $P < 0.05$ ) [11]. Five of 75 aciclovir-treated patients (7%) developed lesions, in comparison with 19 (26%) of 72 persons in the placebo group.

The second, rather small RCT (20 individuals with at least six episodes of HSL/year) found that aciclovir (400 mg twice daily for 4 months) led to 53% fewer clinical recurrences than placebo ( $P = 0.05$ ) and a more than 2.5-fold greater prolongation in the median time to first clinical recurrence (46–118 days;  $P = 0.05$ ) [12].

The pooled analysis of two further RCTs [13] (98 adults with at least four episodes of HSL in the previous year) found that oral valaciclovir 500 mg daily significantly increased the interval to recurrence in comparison with placebo (no recurrence within 4 months: 62% with oral valaciclovir vs 40% with placebo;  $P = 0.041$ ; mean time to recurrence 13.1 weeks with oral valaciclovir vs 9.6 weeks with placebo;  $P = 0.016$ ).

In contrast, two RCTs found no effect of prophylactic antiviral treatment. In 239 skiers with a history of recurrent HSL, no significant differences were observed with regard to the occurrence of herpetic lesions between the active treatment group (800 mg aciclovir twice daily, starting on the day *before* ultraviolet exposure) in comparison with the placebo group – 21 of 93 (23%) with aciclovir versus 21 of 102 (21%) with placebo ( $P = 0.92$ ; 95% CI, not stated) [14].

In another RCT including 248 adults with a history of sun-induced recurrent HSL, famciclovir was administered in different regimens (125, 250, or 500 mg three times a day for 5 days, beginning 48 h *after* artificial ultraviolet exposure) in comparison with placebo [15]. No significant differences were found between the

four groups with regard to numbers of lesions ( $P$  value not reported). However, a dose–response relationship was found between increasing doses of famciclovir and significantly reduced size and duration of the lesions: Only the 500 mg regimen significantly reduced the mean time to healing by 2 days (4 vs 6 days, 33% reduction;  $P = 0.01$ ) and the size of lesions (mean size of lesions;  $P = 0.04$ ; mean time to healing:  $P = 0.01$ ).

A double-blind RCT found that L-lysine monohydrochloride (assumed antiviral activity due to its antagonism of arginine metabolism required in HSV replication) was ineffective administered at daily doses of 624 mg orally, but effective with regard to the recurrence rates when administered at high oral dosages (1248 mg/day). During the treatment period of 24 weeks, 0.89 recurrences per patient (i.e., 0.037 per patient per week) occurred during high-dose treatment, 1.56 recurrences per patient (i.e., 0.065 recurrences per patient per week) during placebo treatment, and 2.27 recurrences per patient (0.095 recurrences per patient and week) in the low-dose treatment [16]. The duration of symptoms was similar to placebo [16].

## Drawbacks

Mild to moderate headache and nausea were the most common adverse effects reported of antiviral treatment. The second RCT provided no information about adverse effects [12]. None of the other RCTs [11–15] found significant differences in frequency or severity of adverse events with the used antiviral drug and placebo.

## Comments

The participants in one RCT were allowed to use paracetamol as concomitant medication and were encouraged to use sunscreens [14]. Sunscreens could be a confounder with the effects of aciclovir in this study, since sunscreens per se could have a preventive effect on herpetic recurrences. A systematic review on this issue was not found. Two small crossover RCTs are available [17,18]. Both found that sunscreen significantly reduced recurrences in individuals with a history of ultraviolet-induced reactivation at 6 days in comparison with placebo: (i) no recurrences occurred in 35 patients with sunscreen versus 27 of 38 (71%) with placebo ( $P < 0.001$ ) [17]; (ii) at a defined UV dose, one recurrence occurred in 19 individuals (5%) with sunscreen versus 11 of 19 (58%) with placebo ( $P < 0.01$ ) [18].

## Implications for clinical practice

Oral antiviral agents, as well as the use of sunscreens, are likely to be beneficial for prevention of labial recurrences. Prophylactic oral antiviral agents may reduce the frequency and severity of attacks in comparison with placebo [11–15]. However, the optimal timing and duration of treatment is uncertain. Topical antivirals are of unknown effectiveness, since no RCTs are available on the effects of prophylactic use of topical antiviral agents.

## Which treatments are effective in treating recurrent oral/labial herpes simplex in the immunocompetent adult?

### Efficacy

A systematic review is currently unavailable. A protocol for a CSR on interventions for treatment of HSL has been registered (dated 2011). Its objective is to review any topical or systemic agents or physical interventions used therapeutically for HSL, in different doses, frequency, and duration of administration. The control may be a placebo, no treatment, or another active intervention [19].



A number of individual RCTs are available both for topical and for systemic treatment of labial recurrences.

### Topical treatment of recurrences

Several RCTs are available on topical aciclovir/penciclovir versus placebo for treatment of clinical manifestations of recurrent HSL in immunocompetent adults [20–30]. Most RCTs found that aciclovir significantly reduced healing time up to 2 days in comparison with placebo (median value to complete healing in placebo: 8 days vs 6 days with aciclovir) [21,22,25–28]. In a small RCT ( $n = 15$ ) with a crossover design, aciclovir in liposomes significantly reduced the time to crusting of lesions in comparison with aciclovir cream (1.8 days vs 3.5 days;  $P = 0.023$ ) [30]. One RCT found no significant difference in healing time between topical aciclovir and placebo [23].

Four RCTs found no significant differences in the duration of pain between aciclovir and placebo [20–23,25], whereas one large RCT on treatment with penciclovir showed a significantly reduced duration of pain (median 3.5 days with penciclovir vs 4.1 days with placebo;  $P < 0.001$ ) [24], as well as a reduced healing time of up to 2 days [24,27].

The combination of 5% aciclovir and 1% hydrocortisone (ME 609; Xerese™; FDA approved since 2009) applied five times per day for 5 days showed a significant benefit in prevention of ulcerative lesion in HSL in an RCT with  $n = 2437$  enrolled patients with a history of recurrent labial herpes [31]. A total of 1443 patients experienced a recurrence and initiated the treatment. Of patients receiving the aciclovir–hydrocortisone combination ( $n = 601$ ), 42% did not develop an ulcerative lesion compared with 35% of patients ( $n = 610$ ) receiving aciclovir ( $P = 0.014$ ) and 26% of patients ( $n = 232$ ) receiving placebo ( $P < 0.0001$ ). Healing times of ulcerative lesions were reduced in the aciclovir–hydrocortisone and aciclovir groups compared with placebo ( $P < 0.01$  for both). The cumulative lesion area for all lesions was reduced 50% in patients receiving the aciclovir–hydrocortisone combination compared with the placebo group ( $P < 0.0001$ ). There were no differences among groups in the number of patients with positive HSV cultures. The side-effect profile was similar among treatments [31].

Topical preparations other than antiviral agent (e.g., local anesthetics, zinc oxide, 1,5-pentanediol, hydrocolloidal wound dressing) have also been suggested in order to reduce the healing time and duration of pain.

One double-blind RCT ( $n = 72$ ) found that 1.8% tetracaine (amethocaine) cream (applied six times per day) significantly reduced the mean time to loss of crusts (5.1 days with tetracaine vs 7.2 days with placebo;  $P = 0.002$ ) and significantly increased the subjective benefit of treatment [32].

One double-blind RCT ( $n = 46$ ) found that zinc oxide/glycine (applied twice an hour during waking hours from the first signs of the herpetic reactivation) significantly reduced time to healing in comparison with placebo (5.0 days with cream vs 6.5 days with placebo;  $P = 0.018$ ) [33].

In one double-blind RCT in  $n = 105$  patients with HSL recurrences, a 25% 1,5-pentanediol gel applied twice a day versus placebo showed a statistically significant superiority ( $P < 0.001$ ) regarding the healing time of the symptoms blistering, swelling, and pain during recurrences. 1,5-Pentanediol is an emulsifying agent with antiviral properties. There was no significant difference in recurrence rate between the two groups ( $P > 0.05$ ) [34].

One multicenter assessor-blinded study in 728 subjects with a history of recurrent HSL compared the efficacy of topical 5% aciclovir cream (applied five times per day) versus a hydrocolloidal

wound dressing (CSP) [35]. Of 351 individuals who experienced an HSL outbreak,  $n = 179$  were randomized to use CSP and  $n = 172$  aciclovir cream 5% at the onset of symptoms until the lesion healed, for a maximum of 10 days. The primary end point was the subject's global assessment of therapy (SGAT: 0, no response; 10, excellent response). The difference in SGAT (7.89 and 8.00, respectively) and in healing times between products was not significant (median, 7.57 days with CSP vs 7.03 days with aciclovir,  $P = 0.37$ ). Both treatments were well tolerated. CSP-treated subjects reported a higher lesion protection and hygiene and lower visibility.

### Systemic treatment of recurrences

Four RCTs were found on systemic antiviral treatment of recurrences in immunocompetent adults [36–38]. The first (including 174 adults with recurrent herpes labialis) found that oral aciclovir (400 mg five times per day for 5 days), taken from the first signs of recurrence (symptoms of labial tingling), significantly reduced the duration of clinical symptoms in comparison with placebo (8.1 days with oral aciclovir vs 12.5 days with placebo;  $P = 0.02$ ) [36]. The second RCT ( $n = 149$ ) compared oral aciclovir (200 mg five times per day for 5 days) started within 12 h of the recurrence with placebo: no significant differences were found with regard to healing time or duration of pain between oral aciclovir and placebo [37]. Two further RCTs (published in the same paper) compared oral valaciclovir (2 g twice per day administered for 1 day only), oral valaciclovir (2 g twice per day on the first day followed by 1 g twice per day on the second day) and placebo in patients over 12 years of age with a history of recurrent HSL [38]. One of these RCTs ( $n = 902$ ) found that both regimens significantly reduced the median duration of vesicular and nonvesicular lesions in comparison with placebo (4.0 days with 1-day treatment,  $P < 0.001$ ; 4.5 days with 2-day treatment with valaciclovir,  $P < 0.009$ , vs 5.0 days with placebo). The other RCT ( $n = 954$ ) found similar results (5.0 days with 1-day treatment,  $P < 0.001$ ; 5.0 days with 2-day treatment with valaciclovir,  $P < 0.001$ , vs 5.5 days with placebo). Neither RCT found a significant difference between 1-day treatment and 2-day treatment with valaciclovir ( $P$  values not reported).

### Drawbacks

#### Topical treatment

No serious adverse events of topical antiviral agents were reported, and similar rates of minor adverse effects occurred in the active treatment groups and placebo groups [20–31]. No adverse effects were reported as a result of topical treatment with 1.8% tetracaine (amethocaine) cream and 1,5-pentanediol [32]. Transient mild to moderate sensations of burning, itching, stinging, or tingling were reported in up to 22% ( $n = 7$ ) of patients treated with zinc oxide, versus 7% ( $n = 2$ ) with placebo [33]. Mild lip bleeding, erythema, and irritation related to the study medication were reported in 7.5% ( $n = 4/53$ ) of patients treated with the hydrocolloid dressing versus 3.8% ( $n = 2/52$ ) with aciclovir.

#### Systemic treatment

The first two RCTs on oral antiviral treatment provided no information about adverse events [37,38]. In the large third and fourth RCTs [38], headache was more common with valaciclovir than with placebo (third RCT: 9% with 1-day treatment; 9% with 2-day treatment with valaciclovir vs 4% with placebo;  $P$  values not reported; fourth RCT: 10% with 1-day treatment; 9% with 2-day treatment

vs 5% with placebo; *P* values not reported) [38]. The other most common adverse events, nausea and diarrhea, were reported equally in all three treatment groups (1-day treatment with valaciclovir, 2-day treatment with valaciclovir, and placebo).

### Comments

Early treatment after onset of the recurrence is apparently feasible, but no RCTs on early versus delayed intervention are available. Firm conclusions about the most feasible timing of systemic antiviral treatment cannot, therefore, be drawn.

### Implications for clinical practice

Data from a number of RCTs comparing topical antiviral agents with placebo in the treatment of recurrences of HSL show discordant results with regard to the duration of pain, but provide stronger evidence that topical penciclovir, aciclovir, and acyclovir-hydrocortisone reduce the healing time. Healing times differed not significantly between aciclovir and a hydrocolloidal dressing (CSP).

One small RCT found limited evidence that topical tetracaine reduced the mean time to scab loss, another accelerated healing time with pentanediol compared with placebo. One small RCT found limited evidence that zinc oxide cream reduced time to healing, but found a higher proportion of mild skin irritation compared with placebo.

RCTs on the systemic treatment of recurrent episodes of HSL provided limited evidence that oral aciclovir and valaciclovir (if taken early at the first symptoms of recurrence) slightly reduced the duration of lesions and pain in comparison with placebo.

### Which treatments are beneficial in primary manifestations of genital herpes simplex in the immunocompetent adult?

#### Efficacy

A systematic review is not available. Three RCTs compared aciclovir (200 mg five times per day for 10 days [39,40] or 5 days [41]) versus placebo [39]. The first RCT [39] (including 119 individuals with primary manifestation of genital herpes) showed that aciclovir significantly reduced the time to complete healing of lesions (12 days with aciclovir vs 14 days with placebo; *P* = 0.005), reduced the formation of new lesions (18% with aciclovir vs 62% with placebo; *P* = 0.001), reduced the duration of pain (5 days with aciclovir vs 7 days with placebo; *P* = 0.05), and reduced viral shedding in comparison with placebo (2 days with aciclovir vs 9 days with placebo; *P* < 0.001). The second RCT (including 31 individuals with primary manifestation of genital herpes) [41] and third RCT [40] (including 31 women and 17 men) with aciclovir (200 mg five times daily for 10 days) confirmed these results.

A systematic review comparing valaciclovir with aciclovir was not found. One large RCT (including 643 individuals with a first episode of genital herpes) compared oral valaciclovir (1000 mg twice daily for 10 days) with oral aciclovir (200 mg five times daily for 10 days) [42]. It found no significant difference between the treatments with regard to healing time (hazard ratio [HR], 1.08; 95% CI, 0.92–1.27), duration of symptoms (HR, 1.02; 95% CI, 0.85–1.22), and duration of viral shedding (HR, 1.00; 95% CI, 0.84–1.18).

### Drawbacks

Adverse effects were rare and similar in the placebo and treatment groups (aciclovir) [40,41]. In a large RCT, headache occurred in

11.5% and nausea in 5.9% of patients treated with aciclovir [42]. There were no differences with regard to adverse events between the aciclovir and valaciclovir groups.

### Comments

In one of the RCTs [39], 30 of 180 participants (17%) were excluded before analysis: 10 because the study protocol was not completed, 12 due to suspected previous infection, and eight because HSV was not isolated [39]. Famciclovir is also recommended for the first clinical episode of genital herpes according to expert guidelines [43].

### Implications for clinical practice

Oral antiviral treatment with aciclovir/valaciclovir in patients with a primary manifestation of genital herpes is effective with regard to the duration of lesions, symptoms, and viral shedding in comparison with placebo. One large RCT found no differences in clinical outcomes between oral aciclovir and valaciclovir.

### Which medical interventions are effective in preventing recurrences of genital herpes simplex in immunocompetent adults?

#### Efficacy

Currently, there is no systematic review, but there is a protocol for a CSR available on oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients (dated from 2011) [9]. Its objectives are to review suppressive oral antiviral treatment of genital herpes with oral aciclovir, famciclovir, or valaciclovir compared with placebo or an antiviral treatment with regard to rate of recurrent episodes of genital herpes and recurrence-free survival as primary outcomes [9].

Based on numerous RCTs, several oral antiviral agents have been suggested for prophylaxis against the reactivation of genital herpes.

#### Aciclovir versus placebo

One nonsystematic review based on two RCTs (*P* = 107) [44] found in the first RCT (*n* = 32) that aciclovir (800 mg/day) reduced recurrences in comparison with placebo at 2 years – no recurrence at 2 years: five of 18 (28%) with aciclovir versus none of 14 (0%) with placebo; absolute risk reduction (ARR), 28% (95% CI, 1–51%) [44]. In the second RCT (*n* = 75), aciclovir (400 mg twice per day) also reduced recurrences in comparison with placebo at 1 year – no recurrence at 1 year: 21 of 48 (44%) with aciclovir versus none of 28 (0%) with placebo (ARR, 44%; 95% CI, 26–56%).

Four other RCTs [45–48] comparing aciclovir (400 mg twice per day) with placebo gained concordant results:

- 1 *n* = 1479 participants – no recurrence at 1 year: 49% with aciclovir versus 5% with placebo; HR, 0.21; 95% CI, 0.16–0.27 [45].
- 2 *n* = 1146 participants – recurrence rate at 1 year: 1.7% with aciclovir versus 12.5% with placebo; *P* < 0.0001 [46]; *n* = 210 participants with continuous aciclovir treatment for 5 years – 53–70% of patients were free of recurrence each year [46].
- 3 *n* = 32 women – aciclovir (for 70 days) reduced viral shedding in comparison with placebo by 95% on days with reported lesions and by 94% on days without lesions [47].
- 4 The fourth RCT (*n* = 1479) [48] compared the suppressive effects of antiviral agents administered once or twice per day in a six-armed protocol (valaciclovir 1000 mg once per day; valaciclovir 500 mg once per day; valaciclovir 250 mg once per day; valaciclovir 250 mg twice per day; aciclovir 400 mg twice per day;

or placebo) with regard to quality of life [49]. All treatment groups (and aciclovir most) significantly improved the health-related quality of life in comparison with placebo after 3 months ( $P < 0.05$ ) [48].

A recent RCT in a total of 3127 evaluable HSV-2-seropositive, HIV-negative, participants enrolled in the USA, Peru, and Africa comparing aciclovir suppressive therapy (400 mg twice per day) with placebo found reduced HSV-2-associated genital ulcer disease and lesional HSV shedding. Aciclovir had a significantly smaller effect on the frequency of genital ulcer disease as well as a smaller effect on the frequency and quantity of lesional HSV DNA in African women and Peruvian men, compared with its effects in men in the USA ( $P < 0.001$ ) [50]. Virus strain variation, differences in aciclovir absorption, or pharmacokinetics may be responsible for these differences. Further studies are required for elucidation of causes and optimization of antiviral prevention of recurrences in these populations.

### **Valaciclovir versus placebo**

One systematic review (published in 1999; search date not reported) [51] based on two RCTs ( $n = 1861$ ) compared suppressive treatment with valaciclovir versus placebo for frequently recurring genital herpes. The first RCT included in the review ( $n = 382$ ) found that valaciclovir (500 mg once per day for 16 weeks) significantly increased the time to recurrence in comparison with placebo (HR, 0.10; 95% CI, 0.11–0.21) [51]. At 16 weeks, 69% of the valaciclovir recipients were recurrence free, in comparison with 9.5% of placebo recipients.

The second RCT ( $n = 1479$  people) compared the suppressive effects of valaciclovir administered once or twice per day in a six-armed protocol (valaciclovir 1000 mg once per day; valaciclovir 500 mg once per day; valaciclovir 250 mg once per day; valaciclovir 250 mg twice per day; aciclovir 400 mg twice per day) versus placebo at 1 year. A dose-dependent effect of valaciclovir was observed in relation to freedom from recurrence in comparison with placebo. Subgroup analysis showed that patients with a history of less than 10 recurrences per year were effectively managed with 500 mg of valaciclovir once daily. One gram of valaciclovir once daily, 250 mg of valaciclovir twice daily, or 400 mg of aciclovir twice daily were more effective in patients with 10 or more recurrences per year. Suppressive treatment with valaciclovir (once or twice daily) significantly improved health-related quality of life in comparison with placebo after 3 months (as measured using a recurrent genital herpes quality-of-life questionnaire;  $P < 0.05$ ) [48,49].

An RCT ( $n = 152$ ;  $n = 109$  receiving valaciclovir 1 g/day vs 43 receiving placebo for 60 days) demonstrated in the intention-to-treat population a 71% reduction in total shedding ( $P < 0.001$ ), a 58% reduction in subclinical shedding ( $P < 0.001$ ), and a 64% reduction in clinical shedding ( $P < 0.01$ ) [52].

Two recent RCTs studied suppressive therapy (valaciclovir 1 g/day vs placebo for 6 months) during the *first year after acquisition* of genital herpes, the time of maximum frequency of reactivation, potential for transmission, and impact on quality of life. The intention-to-treat analysis of the first of the two studies ( $n = 119$  participants enrolled in two centers in the USA) analyzed rates of symptomatic recurrences for valaciclovir and placebo. These were  $1.7 \pm 2.7$  (mean plus/minus standard deviation) and  $3.4 \pm 4.0$  outbreaks per year ( $P = 0.012$ ). Time to first recurrence was  $80 \pm 47$  days for valaciclovir and  $54 \pm 49$  days for placebo ( $P = 0.001$ ). The differences in favor of valaciclovir were greatest in patients with confirmed HSV-2 infection. The Recurrent Genital Herpes Quality

of Life score in HSV-2-infected patients rose  $11.9 \pm 11.1$  points for valaciclovir and  $5.9 \pm 9.1$  points for placebo ( $P = 0.040$ ) [53].

The second RCT with  $n = 384$  subjects enrolled in 75 centers in the USA, Canada, Argentina, Brazil, and Chile confirmed these findings: 43% of subjects on placebo and 71% of subjects on valaciclovir were recurrence free at 24 weeks ( $P < 0.001$ ), mean number of recurrences per month was 0.11 for valaciclovir and 0.48 for placebo,  $P < 0.001$ . Adverse events were comparable in the valaciclovir and placebo arms [54].

### **Famciclovir versus placebo**

One systematic review [51] based on two RCTs ( $n = 830$ ) found that famciclovir significantly increased the median time to first recurrence in comparison with placebo. In the first RCT ( $n = 455$ ), famciclovir (250 mg twice per day, 125 mg three times per day, or 250 mg three times per day for 1 year) increased the median time to first recurrence significantly in comparison with placebo (11 months with famciclovir 250 mg twice per day, vs 10 months with famciclovir 250 mg three times per day, vs 8 months with famciclovir 125 mg three times per day, vs 1.5 months with placebo). In the second RCT ( $n = 375$ ), female recipients received famciclovir (125 mg twice per day, 125 mg four times per day, 250 mg twice per day, 250 mg four times per day, or 500 mg four times per day, or placebo for 4 months). Famciclovir 250 mg twice per day was found to be the most effective dosage for reducing recurrences [51]. In comparison with placebo, significant numbers of famciclovir recipients were free of recurrences at 4 months (78% with 250 mg twice per day vs 42% with placebo).

### **Valaciclovir versus famciclovir**

Two RCTs compared famciclovir (250 mg b.i.d.) and valaciclovir (500 mg/day) administered as daily suppressive therapy for individuals with genital herpes [55]. Study 1 (including 320 participants) compared the clinical effect of the drugs given for 16 weeks; study 2 compared the virological effect of the drugs given for 10 days in 70 HSV-2-seropositive patients. In study 1, the time to first recurrence was similar in the famciclovir and valaciclovir recipients, with an HR of 1.17 (95% CI, 0.78–1.76), but the time to the first virologically confirmed recurrence was shorter among famciclovir recipients (HR, 2.15; 95% CI, 1.00–4.60). In study 2, HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valaciclovir recipients (relative risk, 2.33; 95% CI, 1.18–4.89) [55].

### **Drawbacks**

Daily treatments with aciclovir, famciclovir, and valaciclovir were well tolerated [45,56]. The safety profiles of all of the treatments were comparable.

The aciclovir recipients were followed for up to 7 years, and the famciclovir and valaciclovir recipients for up to 1 year [56]. Nausea and headache were infrequent, and participants rarely discontinued treatment due to adverse effects. No evidence was found that suppressive daily treatment with aciclovir results in the development of aciclovir resistance during or after stopping treatment in healthy adults [56].

### **Comments**

Further comparative trials of antiviral drugs for the suppression of genital herpes recurrences should be conducted, as aciclovir and penciclovir appear to have different abilities to abrogate HSV reactivation.



### Implications for clinical practice

Oral antiviral maintenance treatment in patients with a history of frequent recurrences is of benefit. Daily maintenance treatment with oral antiviral agents reduces the frequency of recurrences, and improves the quality of life in comparison with placebo.

Valaciclovir appears to be somewhat better than famciclovir for suppressing genital herpes and associated shedding. Suppressive treatment with valaciclovir during the first year after acquisition of the infection, when recurrences are most frequent, increases significantly the patients' quality of life.

### Are antiviral interventions effective in preventing virus shedding in herpes simplex virus-seropositive asymptomatic immunocompetent adults?

#### Efficacy

Virus shedding occurring in HSV-seropositive asymptomatic individuals contributes to virus transmission. There are two RCTs, each with a crossover design after a washout period (one with valaciclovir, one with famciclovir), investigating virus shedding as primary outcome in asymptomatic HSV-seropositive subjects [57,58].

The first RCT compared the effect of valaciclovir 1 g/day for 60 days versus placebo on asymptomatic virus shedding in 73 immunocompetent, HSV-2-seropositive subjects without a history of symptomatic genital herpes infection.

Valaciclovir significantly reduced shedding during subclinical days compared with placebo (mean, 1.5% vs 5.1% of subclinical days ( $P < 0.001$ ), a 71% reduction). Eighty-four percent of subjects had no shedding while receiving valaciclovir versus 54% of subjects on placebo ( $P < 0.001$ ). Valaciclovir was not associated with any safety risk compared with placebo [57].

In another RCT, famciclovir (250 mg b.i.d. for 42 days) reduced genital and oral HSV shedding from 11.4% of days during the placebo period (42 days) to 4.7% of days during famciclovir therapy in HSV-seropositive asymptomatic persons without evidence of clinical disease. The reduction was greater in participants with a history of genital herpes (74%) than in those without such a history (30%). In multivariate analyses, famciclovir protected against total (clinical and subclinical) genital shedding among persons with a clinical history of genital herpes (RR, 0.23; 95% CI, 0.15–0.35;  $P < 0.001$ ). Among HSV-2 seropositive participants without a history of genital herpes, 60% had HSV detected in the genital area at least once during the study. Famciclovir therapy did not result in a statistically significant reduction in total HSV shedding in participants without a history of genital herpes [58].

Three separate but complementary open-label crossover studies of 4–7 weeks (separated by 1 week wash-out) compared (i) no medication with aciclovir 400 mg b.i.d. (standard-dose aciclovir), (ii) valaciclovir 500 mg/day (standard-dose valaciclovir) with aciclovir 800 mg three times daily (high-dose aciclovir), and (iii) standard-dose valaciclovir with valaciclovir 1 g three times per day (high-dose valaciclovir). Short bursts of subclinical genital HSV reactivation were frequent, even during high-dose antiherpes therapy. Of 113 participants randomized, 90 were eligible for analysis of the primary endpoint. Of 23 605 collected swabs, 1272 (5.4%) were HSV positive. The frequency of HSV shedding was significantly higher in the no medication group ( $n = 384$ , 18.1% of swabs) than in the standard-dose aciclovir group (25, 1.2%; incidence rate ratio [IRR], 0.05, 95% CI, 0.03–0.08). High-dose aciclovir was associated with less shedding than standard-dose valaciclovir: 198 (4.2%) versus 209 (4.5%); IRR 0.79; 95% CI, 0.63–1.00. Shedding

was less frequent in the high-dose valaciclovir group than in the standard-dose valaciclovir group: 164 (3.3%) versus 292 (5.8%); 0.54; 95% CI, 0.44–0.66. The number of episodes per person-year did not differ significantly for standard-dose valaciclovir (22.6) versus high-dose aciclovir (20.2;  $P = 0.54$ ), and standard-dose valaciclovir (14.9) versus high-dose valaciclovir (16.5;  $P = 0.34$ ), but did for no medication (28.7) and standard-dose aciclovir (10.0;  $P = 0.001$ ).

Median episode duration was longer for no medication than for standard-dose aciclovir (13 h vs 7 h;  $P = 0.01$ ) and for standard-dose valaciclovir than for high-dose valaciclovir (10 h vs 7 h;  $P = 0.03$ ), but did not differ significantly between standard-dose valaciclovir and high-dose aciclovir (8 h vs 8 h;  $P = 0.23$ ). Eighty percent of episodes were subclinical in all study groups. Except for a higher frequency of headaches with high-dose valaciclovir ( $n = 13$ , 30%) than with other regimens, all regimens were well tolerated [59].

#### Drawbacks

Treatments with aciclovir, valaciclovir, famciclovir, and placebo were all well tolerated. In contrast to the RCT with valaciclovir [57], famciclovir therapy did not result in a statistically significant reduction in total HSV shedding in participants without a history of genital herpes [58]. In recent open label crossover studies, despite high-dose antiviral treatment, short bursts of subclinical viral shedding were reported [59].

#### Comments

Asymptomatic viral shedding is considered to be the primary means of transmitting HSV to sexual partners. The results of these studies show differences between antiviral agents at the given dose to suppress viral shedding in asymptomatic subjects with no history of symptomatic genital herpes infection. Reduction of virus shedding may be achieved by chemoprophylaxis with valaciclovir even in asymptomatic subjects with no history of symptomatic genital herpes infection; however, short bursts still occur. Whether a reduced frequency and duration of viral shedding is sufficient to reduce the risk of transmission to an HSV-seronegative partner will require further studies.

Barrier methods are used for reduction of virus transmission. A systematic review based on six studies ( $n = 5384$  individuals who were HSV-2 negative at baseline) showed in a multivariate model a significant decrease in risk of HSV-2 acquisition with a 25% increase in condom use (HR, 0.93; 95% CI, 0.85–0.99;  $P = 0.01$ ) while the aggregate HR for 100% versus 0% condom use was 0.70 (95% CI, 0.40–0.94) [60].

In addition to approaches to control virus shedding in HSV-positive individuals, vaccines for HSV-negative subjects are being developed. Currently, several preclinical and clinical studies with different candidate vaccines (glycoprotein D-, peptide-, and DNA-based) and adjuvants are under investigation in HSV-negative as well as HSV-positive individuals to evaluate their benefit for new acquisition of infection as well as disease suppression with diverging results [61–65].

### Implications for clinical practice

To this point, no antiviral chemoprophylaxis provides complete protection from subclinical virus shedding and disease transmission. Barrier methods such as condoms are beneficial to reduce viral transmission. Vaccines are under development, but are not yet available in clinical practice.



## Are antiviral interventions effective in preventing maternal genital herpes simplex virus recurrences and neonatal infections?

### Efficacy

Among women with recurrent genital HSV, nearly 75% can expect at least one recurrence during pregnancy, and about 14% of women will have prodromal symptoms (early symptoms indicating the onset of an attack) or clinical recurrence at delivery [66]. Transmission of the virus from mother to fetus typically occurs by direct contact with the virus in the genital tract during delivery. The estimated incidence of neonatal herpes infection is broad, ranging from 5 to 80 per 100 000 live births [66]. To reduce neonatal transmission, it is currently recommended that a cesarean delivery be offered to all women with active genital lesions or prodromal symptoms at delivery [66].

A CSR on antiviral prophylaxis for preventing maternal genital HSV recurrence and neonatal infection [66] found seven RCTs (1249 participants) which met its inclusion criteria: five trials compared aciclovir (in doses of 400 mg p.o. t.i.d. or 200 mg p.o. four times daily) with placebo or no treatment. Two trials compared valaciclovir (500 mg p.o. b.i.d.) with placebo.

The  $I^2$  index indicates the degree of heterogeneity in the meta-analysis. Women who received antiviral prophylaxis (beginning from 36 weeks' gestation) were significantly less likely to have a symptomatic recurrence of genital herpes at delivery (RR, 0.28; 95% CI, 0.18–0.43,  $I^2 = 0\%$ ) and were also significantly less likely to have a cesarean delivery for genital herpes (RR, 0.30; 95% CI, 0.20–0.45,  $I^2 = 27.3\%$ ). They were significantly less likely to have HSV detected at delivery (RR, 0.14; 95% CI, 0.05–0.39,  $I^2 = 0\%$ ). The effect of antepartum antiviral prophylaxis on neonatal herpes could not be estimated. There were no cases of symptomatic neonatal herpes in the studies included in either the treatment or placebo groups [66].

### Drawbacks

A previous systematic review based on three RCTs dealing with the treatment of genital herpes in pregnant women found no evidence of adverse effects of aciclovir in the women or the newborns [67].

### Comments

Antiviral agents are not approved for the treatment of genital herpes in breastfeeding and pregnant women.

A recent CSR found the risk of neonatal herpes low in both treatment groups (antiviral and placebo). There is insufficient evidence to determine if antiviral prophylaxis for women with a history of genital herpes reduces the incidence of neonatal herpes. Antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for symptomatic genital herpes. The risks, benefits, and alternatives to antenatal prophylaxis should be discussed individually with women who have a history and prophylaxis initiated in women who desire intervention [66].

## What are effective therapeutic interventions for the treatment of recurrent genital herpes simplex in immunocompetent adults?

### Efficacy

#### Aciclovir versus placebo

No systematic reviews were found. In one nonsystematic review ( $n = 650$  people) [44] in comparison with placebo oral aciclovir (200 mg five times per day or 800 mg twice per day, administered early at the first signs of recurrence for 5 days) reduced duration of

lesions (5 days with aciclovir vs 6 days with placebo) and the duration of viral shedding (1 day with aciclovir vs 2 days with placebo) [44].

In another RCT ( $n = 131$  individuals with more than three recurrences during the previous 12 months, followed at least until the next recurrence), aciclovir (800 mg three times per day for 2 days) significantly reduced the duration of episodes (median duration: 4 days with aciclovir vs 6 days with placebo;  $P < 0.001$ ), the duration of lesions (median duration: 4 days with aciclovir vs 6 days with placebo;  $P < 0.001$ ), and viral shedding (median duration: 25.0 h with aciclovir vs 58.5 h with placebo;  $P = 0.04$ ) [68]. The benefit was marked if the treatment was initiated early at the first signs of recurrence [69].

#### Valaciclovir versus placebo

One systematic review (based on one RCT, including 987 patients) [51,70] on patient-initiated treatment with oral valaciclovir (500 or 1000 mg twice per day for 5 days) versus placebo found a decreased duration of the lesion and accompanying discomfort (median duration: 4 days with valaciclovir vs 6 days with placebo; HR, 1.9; 95% CI, 1.6–2.3), a decreased duration of viral shedding (median duration: 2 days with valaciclovir vs 4 days with placebo; HR, 2.9; 95% CI, 2.1–3.9), and an increased rate of aborted recurrences in comparison with placebo (aborted recurrences: 31% with valaciclovir vs 21% with placebo; RR, 1.5; 95% CI, 1.1–1.9) [70]. No differences in the outcomes were noted between the two groups who received valaciclovir (500 mg b.i.d. vs 1000 mg b.i.d.) for 5 days. The lower dosage is therefore recommended.

#### Valaciclovir versus aciclovir/valaciclovir

One systematic review (based on one RCT;  $n = 739$ ) [71] on valaciclovir versus aciclovir showed that the two regimens (valaciclovir 500 mg b.i.d.) and aciclovir (200 mg five times per day) given for 5 days were equivalent with regard to healing time, symptom duration, and viral shedding [51].

No differences were observed between a 3-day and 5-day regimen with valaciclovir (500 mg twice per day;  $n = 531$  individuals with more than six recurrences per year) with regard to episode duration (4.7 days with the 3-day treatment vs 4.6 days with the 5-day treatment with valaciclovir; significance not reported) or aborted recurrences (27% with the 3-day treatment vs 21% with the 5-day treatment with valaciclovir (RR, 1; 95% CI, 0.92–1.65)) [72]. Initiating treatment within 6 h of the first symptoms was associated with a greater likelihood of aborted recurrences than initiation later than 6 h (odds ratio [OR], 1.93; 95% CI, 1.28–2.9) [72]. Another RCT (including 800 individuals with more than four recurrences per year) found concordant results with 3-day and 5-day treatment with valaciclovir (500 mg twice daily) [73].

#### Famciclovir versus placebo

One systematic review on famciclovir versus placebo (based on one RCT,  $n = 467$ ) [51,74] found that patient-initiated oral treatment with famciclovir (125 mg twice per day, 250 mg twice per day, or 500 mg twice per day for 5 days) led to significant reductions in the healing time (median 3.8 days for famciclovir recipients vs 4.8 days for placebo recipients), the duration of viral shedding (1.7 days with famciclovir vs 3.3 days with placebo), and the duration of symptoms (3.2 days with famciclovir vs 3.7 days with placebo;  $P$  values not reported) [74]. Famciclovir (125 mg twice daily) was effective, and higher doses did not confer any additional benefit.

In a recent RCT with a total of 299 patients with recurrent genital herpes (66% female, median age 37 years) treatment consisted either of 1-day famciclovir 1000 mg twice-daily ( $n=201$ ) or placebo ( $n = 98$ ). In the modified intent-to-treat population, there were similar outcomes for famciclovir and placebo in the estimated median time to healing of nonaborted genital herpes lesions (5.38 days for famciclovir and 4.79 days for placebo – median of treatment differences 0.26 days; 95% CI,  $-0.40$  to  $+0.98$ ;  $P = 0.416$ ) [75].

#### **Famciclovir versus aciclovir**

No significant differences were found in one RCT ( $n = 204$ ) between oral famciclovir and aciclovir with regard to the time to healing (mean: 5.1 days with famciclovir vs 5.4 days with aciclovir; mean difference,  $+0.3$  days; 95% CI,  $-0.3$  to  $+0.8$  days) [76].

#### **Novel drugs**

New drugs for the treatment of recurrent genital herpes have been investigated; for example, topical resiquimod (a Toll-like receptor 7/8 antagonist) and helicase–primase inhibitors (potent inhibitors of HSV-replication).

In an RCT with vehicle (39 subjects) versus resiquimod (0.01% gel two times per week over 3 weeks, 43 subjects), no difference between the groups was observed with respect to time to healing (median of 7.0 days (vehicle) versus median of 6.5 days (verum), respectively) and time to cessation of viral shedding (median of 7 days vs median of 5 days). Additionally, no significant effects on recurrence rates were observed in the phase III studies, resulting in the discontinuation of the development [77].

In contrast, 3-day or 1-day courses of ASP2151 (a helicase–primase inhibitor) appear to be effective and safe options for treatment of episodes of recurrent genital herpes demonstrated in an RCT that assessed the safety and efficacy of ASP2151 for episodic therapy of recurrent genital herpes. Participants self-initiated treatment with ASP2151 (100, 200, or 400 mg daily for 3 days), ASP2151 (1200 mg as a single dose), placebo for 3 days, or valaciclovir (500 mg twice daily for 3 days). Of 695 adults enrolled, 437 experienced a recurrence and received study drug. Median time for lesion healing was 139.8 h with placebo, 119.6 h with ASP2151 (100 mg; HR, 1.40;  $P = 0.065$ ), 106.2 with ASP2151 (200 mg; HR, 1.40;  $P = 0.081$ ), 115.9 with ASP2151 (400 mg; HR, 1.25;  $P = 0.25$ ), 102.1 with ASP2151 (1200 mg; HR, 1.72;  $P = 0.007$ ), and 113.9 with valaciclovir (500 mg twice daily; HR, 1.42;  $P = 0.077$ ), indicating improvement in all treatment groups except ASP2151 (400 mg). Incidence of treatment-emergent adverse events was similar across groups [78].

#### **Drawbacks**

Adverse effects (mostly headache and nausea) were rare and occurred at similar frequencies in all of the treatment groups (aciclovir, valaciclovir, famciclovir, placebo) [51].

#### **Comments**

Antiviral agents are not approved for the treatment of genital herpes in breastfeeding and pregnant women. One systematic review based on three RCTs dealing with the treatment of genital herpes in pregnant women found no evidence of adverse effects in either the women or the newborn [67].

#### **Implication for clinical practice**

Oral antiviral treatment (aciclovir, famciclovir, valaciclovir) initiated at first symptoms of recurrence (e.g., within 6 h) [72] is effective

with regard to total lesion clearance in the immunocompetent adult. They reduce the duration of lesions and viral shedding and increase the rate of aborted recurrences in comparison with placebo in individuals with recurrent genital herpes. Aciclovir, famciclovir, and valaciclovir are similarly effective in reducing symptom duration, lesion healing time, and viral shedding. The benefit was marked if treatment was initiated early, at the first signs of recurrence [69,72]. There is clinical evidence for effectiveness for a helicase–primase inhibitor from clinical studies; however, it is not available yet in clinical practice.

#### **Key points**

- For primary manifestations of oral/labial herpes (which may be severe), antiviral agents (such as aciclovir) are likely to be beneficial with regard to the mean time required for healing.
- Recurrences of herpes simplex labialis are common, but their frequency can be significantly reduced with prophylactic oral treatment with antiviral agents. The optimal timing and duration of treatment are uncertain.
- In reactivated herpes labialis, there is some evidence that topical penciclovir and aciclovir reduce the healing time.
- Oral aciclovir and valaciclovir (if taken early at the first symptoms of recurrence of labial herpes) may reduce the duration of lesions and pain.
- Oral antiviral treatment in the primary manifestation of genital herpes reduces the duration of lesions, symptoms, and viral shedding.
- Daily suppressive treatment with oral antiviral agents (aciclovir 400 mg twice per day, famciclovir 250 mg twice per day, or valaciclovir 500 mg once per day) reduces the frequency of recurrences. In patients with 10 or more recurrences per year, 1 g of valaciclovir once daily, 250 mg of valaciclovir twice daily, or 400 mg of aciclovir twice daily were more effective. Valaciclovir appears to be somewhat better than famciclovir in suppressing genital herpes and the associated shedding.
- Suppressive daily treatment with aciclovir in individuals with a history of recurrent herpes with aciclovir does not result in resistant HSV strains during or after the cessation of treatment in immunocompetent adults.
- Antiviral suppressive treatment can reduce virus shedding from asymptomatic subjects; however, short bursts of subclinical virus shedding occur despite high-dose antiviral treatment.
- There is insufficient evidence to determine if antiviral prophylaxis for women with a history of genital herpes reduces the incidence of neonatal herpes.
- Antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for symptomatic genital herpes.
- In a clinically manifest recurrence of genital herpes, aciclovir, famciclovir, and valaciclovir are similarly effective in reducing symptom duration, lesion healing time, and viral shedding.
- No serious adverse events associated with topical antiviral agents (aciclovir, valaciclovir, or famciclovir) have been reported.
- Key research gaps in the field of herpes simplex include trials on interventions in primary oral/labial herpes simplex in the immunocompetent adult, trials to determine the maximal tolerable interval between the onset of disease and the start of treatment, and the optimal timing and duration of treatment to prevent recurrences.

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# Leprosy

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## Background

### Clinical scenario

A 32-year-old man presented to the dermatology clinic with a rash. He had developed a single, raised, erythematous patch on his right upper arm 2 months previously, but had ignored it initially. Recently, he had noticed several new lesions developing on his right arm. The lesions were getting bigger and lighter in color, and he was unable to feel any sensation when he pressed on them. There were no other symptoms, and he was otherwise well. He was born in Madagascar and had moved to the UK 5 years previously. No one in his family had leprosy or tuberculosis. Examination revealed multiple well-demarcated, hypopigmented patches and plaques of different sizes on his right upper arm, with loss of pain and light touch sensation (Figure 49.1). There was no evidence of peripheral nerve thickening or loss of function. Histological examination of a skin smear from one of the lesions showed well-defined granuloma with epithelioid cells and a dense, lymphocytic infiltrate, but no acid-fast bacilli. The clinical and histological findings were consistent with a diagnosis of polar tuberculoid (TT) leprosy. When informed of his diagnosis, the patient mentioned that he had heard that leprosy could now be treated with a single dose of antibiotics. He had also read that some patients with leprosy also took steroids with their antibiotics to protect their nerves from permanent damage, and he wanted to be sure that this would be beneficial because he was concerned about the side effects of long-term steroids.

### Definition

Leprosy (from the Greek *lepros*, scaly, scabby, rough) is a chronic infectious granulomatous disease due to *Mycobacterium leprae* [1]. Most people exposed to the organism are able to mount an appropriate immune response and do not develop leprosy, and those who do usually present with single lesions, which often heal without treatment. In a small proportion, however, the lesion may progress to overt disease, the severity of which depends on the host's cell-mediated immune (CMI) response to *M. leprae*. Leprosy is classified according to the degree and type of host immune response as indeterminate (I), tuberculous pole (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous (LL) pole [2].

For treatment purposes, patients are defined as paucibacillary (PB), with five or fewer skin lesions, or multibacillary (MB), with six or more skin lesions. PB leprosy includes TT and BT leprosy, while MB leprosy includes BB, BL, and LL patients [3]. Single-lesion leprosy is often defined separately as a subgroup of PB leprosy, as the treatment is different. In 2000, around 39% of leprosy patients worldwide were classified as MB, 52% as PB (two to five skin lesions), and 9% as having a single lesion [4].

Indeterminate leprosy (I) is considered to be the early stage of leprosy, which can self-heal and may be underdiagnosed. The lesions are vague, hypopigmented macules without definite anesthesia and/or nerve enlargement. In TT leprosy, however, the lesions may be hypopigmented or erythematous, with loss of pain, touch, hot and cold sensations, and lack of sweating due to sympathetic nerve damage. Skin smears often yield few or no bacilli, and the lesions may heal spontaneously. In borderline leprosy, the skin lesions become more numerous and larger, with less well-defined margins, and nerve damage becomes more prominent. In lepromatous leprosy, the overwhelming bacterial load and the limited host immune response results in generalized multisystem infection which, if left untreated, results in severe multiorgan damage. The skin lesions are larger, less well defined, symmetrical, more infiltrated, and often develop into plaques and nodules. The patient may present with extensive sensory and motor nerve damage. The nerves commonly affected are the ulnar and median (leading to claw hand), radial (wrist drop), common peroneal (foot drop), posterior tibial (claw toes), the fifth (corneal sensation) and seventh (facial palsy) cranial nerves, cutaneous sensory nerves especially near skin lesions, and auricular nerves. In advanced cases, the patients may present with loss of eyebrows and eyelashes, nasal cartilage damage with collapsed nose, epididymo-orchitis, and iritis, which may progress to blindness. Other forms of leprosy, such as primary neuritic leprosy without skin lesions, are also recognized and can be diagnosed by nerve biopsy [1].

Reactions in leprosy refer to episodes of acute inflammation of skin lesions, nerves or other body parts. Type I reactions (T1R), or reversal reactions, occur in borderline leprosy due to spontaneous fluctuations in the host CMI response to *M. leprae*, and can occur before, during, or after treatment, making it difficult to distinguish from relapse [5,6]. Patients present with swelling of the limbs and



**Figure 49.1** Multiple well-demarcated, hypopigmented patches and plaques of different sizes on the right upper arm in a 32-year-old patient.

face and the appearance of new skin lesions, which can ulcerate and scar. Neuritis, particularly involving nerves that are already enlarged, can occur either insidiously and painlessly or as a severe painful episode and may result in permanent nerve damage if not treated promptly. The lesions show infiltration of lymphocytes and monocytes, with elevated levels of interferon gamma. The risk of T1R is associated with facial lesions and more extensive disease [7]. The greatest risk of developing T1R is within the first year of starting treatment and is more severe at the tuberculoid end of the spectrum. With multidrug therapy (MDT), the risk of T1R is estimated at 7–20% in PB and 39–48% in MB patients [8]. It has been proposed that the use of more potent antileprosy drugs increases the risk of T1R by releasing large quantities of *M. leprae* antigens due to more effective killing of the organism, causing an exaggerated host immune response [9].

Erythema nodosum leprosum (ENL) describes the development of tender red papules and nodules on the skin and sometimes in the nerves and eyes of patients at the lepromatous end of the disease [5,10]. The lesions develop over a few hours and last a few days, and, unlike T1R, usually recur. They can coalesce to form large plaques and may even ulcerate. ENL occurs due to deposition of immune complexes formed by *M. leprae* antigens together with dysfunction of the host CMI response. Increased levels of tumor necrosis factor- $\alpha$  may have a role in the pathogenesis. The severity of ENL varies tremendously from asymptomatic episodes to gross prostration and even death. Systemic symptoms are often present and include fever, malaise, swelling of the hands and feet, and lymphadenitis. The joints, eyes, testes, liver, spleen, and kidneys may also be involved in severe cases. With clofazimine-containing multidrug regimens, ENL accounts for <1% of all reactions in many large-scale postsurveillance studies [11].

### Incidence/prevalence

The global prevalence of leprosy had declined steadily from its peak of 12 per 100 000 population in 1985 to less than one case per 100 000 by the end of 2000 [4]. Trends in new cases detected globally have also been falling since 2001. At the end of 2000, there were around 5.5 million cases registered for treatment globally, with 719 330 new cases detected that year [4]. Of the 122 countries in which leprosy was endemic in 1985, by the end of 2005 all but six countries (Brazil, Democratic Republic of the Congo, Madagascar, Mozambique, Nepal, and Tanzania) reported a prevalence of less than 1 per 10 000 [12]. In 2002, more than 620 000 new cases were detected, whereas in 2008 there were approximately 249 000 cases. In early 2009, the global prevalence of leprosy was approximately 213 000 cases [13]. It is estimated that over 14 million leprosy patients globally have been cured through MDT.

### Etiology

Progress in leprosy research has been slow, because it has not been possible to cultivate the organism in artificial media; most research is currently performed on the mouse footpad model [14]. The organism is considered to be of high infectivity but low pathogenicity and is rarely fatal. Humans are the main reservoir of infection, but the organism has been found in several primate species and armadillos. *M. leprae* is a rod-shaped, slightly curved, Gram-positive, obligate intracellular organism. The genome of *M. leprae* was published in 2000 and there are very few differences in genomes from *M. leprae* strains isolated from different geographical regions worldwide [15]. It is found mainly in clumps known as globi inside macrophages, and multiplies very slowly, with a generation time of around 12 days. *M. leprae* has a long and variable incubation period, ranging from 1 year to more than 20 years. The optimal temperature for growth is 27–30 °C, which explains its predilection for cooler parts of the human body. The mode of transmission of infection still remains speculative, but it is strongly suspected to involve the respiratory tract, since nasal secretions from infected individuals carry large numbers of the organisms.

Risk factors for leprosy remain poorly understood, but low socioeconomic status, overcrowding, nutritional status, and immune response all play an important role. Household contacts have a higher risk of developing leprosy, particularly if the index case has MB leprosy rather than PB leprosy, and children have a higher risk in comparison with adults [16]. Genetic factors may also influence susceptibility to leprosy and/or progression to overt disease. For example, allelic variants at the human homologue of the mouse natural resistance-associated macrophage protein 1 (Nrp1) gene have been found to be associated with susceptibility to tuberculosis and leprosy in humans [17]. The Nrp1 protein is an integral membrane protein expressed exclusively in the lysosomal compartment of monocytes and macrophages [18]. There is also a strong association between the HLA-DR2 allele and tuberculoid leprosy in ethnically diverse populations and between HLA-DQ1 and lepromatous leprosy [14,17,19]. Other studies have shown an increased risk of leprosy within certain families, high concordance rates among identical twins, and identification of genetic markers on chromosome 10 in linkage studies in south India [17].

### Prognosis and complications

Completion of the antileprosy treatment recommended by the World Health Organization (WHO) leads to cure in almost all cases, with an estimated relapse rate of less than 1% for both PB and MB leprosy [20]. Relapse is defined as reappearance of the

disease, gradual worsening of existing lesions, appearance of new skin lesions, thickened, tender nerves, or muscle paralysis after successful completion of the appropriate treatment and can occur many years after treatment completion. Relapse is mainly diagnosed clinically, although some cases may be identified by routine skin smear tests during posttreatment surveillance, and can be difficult to distinguish from late reactions. A delay in detecting relapse, which often occurs because patients falsely assume they have been cured [21], can lead to further nerve damage and deformities.

However, the main complication of leprosy is the severe disfigurement and deformity that occurs and progresses even after treatment completion. The International Classification of Impairment, Disease and Handicap emphasizes that deformities, defined as alteration in the form, shape, or appearance of parts of the body, result in impairment and not disability [22]. Disability is defined as any restriction or lack of ability to perform in the manner or within the range considered normal for a human being as a result of impairment. The risk of disability in leprosy is complex and associated with age, sex, occupation, classification, and duration of disease, development of reactions, site of lesions, method of case detection, geographic and socio-economic factors, treatment type, educational attainment, and ethnicity [23]. Early identification of the disease is very critical for effective control and disability limitation. A recent study in Nigeria, which used the incidence of disability grade 2 among the new cases as a comparator, found that complementing routine practice with household contact examination to be the most cost-effective approach to identify new leprosy cases [24].

Deformities in leprosy result from *M. leprae* infection, reactions, and relapse, all of which can cause irreversible nerve damage. Neurophysiological changes indicating axonal and demyelinating processes during both T1R and T2R were detected during a clinical trial of steroid treatment effectiveness [25]. The subsequent loss of sensory, motor, and/or autonomic modalities to peripheral limbs often leads to trauma and ulceration of areas supplied by the nerves, eventually leading to gross deformities and even loss of the limb. Psychosocial disabilities are also common and arise from the chronic nature of the disease, the unsightly mutilations that occur, and the stigma associated with leprosy. Thus, loss of confidence, feelings of inadequacy, low self-esteem, anxiety, and frank depression are common among leprosy patients, who are also more likely to be unmarried, divorced, unemployed, and homeless [21]. Another group among whom the prevalence of dementia and depression is particularly high consists of the long-term institutionalized older leprosy patients, as was found in a study conducted in Taiwan [26].

In 1969, the WHO redefined its five-point classification of disability to three grades to facilitate its use by field workers worldwide, and simplified it further in 1988 to two grades only (Table 49.1) [23], with the primary aim of collecting data regarding disability for administrative purposes. In 1995, the global prevalence of grade 2 disability among leprosy patients was estimated at 1–2 million, compared with 3.5 million in 1975 and 3.9 million in 1966. By 2000, of almost 700 000 new cases with information on disability status, only 4% had grade 2 disabilities at presentation [4].

## Diagnostic tests

The diagnosis of leprosy is based principally on the clinical features and can be confirmed by skin smears or biopsy. Leprosy should be suspected in any patient presenting with an anesthetized skin lesion, with or without nerve involvement. Sensory loss to pinprick

and/or light touch is a typical feature of leprosy [17]. The WHO defines a case of leprosy as involving one or more of the following features in anyone who has not completed antileprosy treatment:

- hypopigmented or reddish skin lesion(s) with sensory loss;
- involvement of the peripheral nerves, with thickening or loss of sensation in the area supplied by the nerve;
- skin smear positive for acid-fast bacilli [27].

When performed properly, skin smears can help confirm the diagnosis of leprosy, aid correct classification, monitor treatment progress, and diagnose relapse. The bacterial load can be estimated and expressed using the logarithmic Ridley scale or bacterial index (BI; grades 0–6) based on the number of bacilli seen in an average microscopic field using an oil immersion lens [28]. The morphological index (MI) can be used to determine the percentage of live organisms – a score of zero means that patient is noninfectious.

A biopsy of the skin lesion may help confirm the diagnosis, improve research, and allow culture of *M. leprae* in mouse footpads. However, the sensitivity is poor, because biopsies can yield negative results despite obvious clinical signs. Leprosy lesions are characterized by the formation of granulomas, which vary from the epithelioid type at the tuberculous end to the “foamy” cell type (macrophages filled with *M. leprae*) at the lepromatous end. Immunohistopathological staining for *M. leprae* antigens, such as phenolic glycolipid-1 (PGL-1), have been shown to be very specific, but are still in the developmental stage [29].

The lepromin skin test, which involves injecting inactivated *M. leprae* antigens under the skin, can be used to aid disease classification and predict the type of disease a person is likely to develop, as it measures the host's CMI response against *M. leprae* antigens [17]. The site of injection is examined at 3 days and again at 3–4 weeks after injection for reaction induration. A positive test would suggest the development of leprosy at the tuberculoid end of the spectrum, while a negative test would favor lepromatous leprosy.

Other diagnostic tests have been developed and are currently mainly used for research and epidemiological studies, but many show promise for future use in rapid diagnosis, monitoring therapeutic responses, and early diagnosis of relapse. Serological tests include measurement of anti-PGL-1 antibodies in blood or urine. Although these antibodies are often absent at the tuberculoid end of the spectrum, they may play an important role in early detection of relapse in MB patients and in detection of subclinical infection, because they can be present before the onset of clinical symptoms [14]. A systematic review incorporating 26 studies has affirmed that with a simple and robust technique the use of PGL-1 serology is viable [30]. Detection of *M. leprae* in tissues, using several polymerase chain reaction methods and probes targeting stretches of *M. leprae* DNA or ribosomal RNA, has also been developed and is

**Table 49.1** The 1988 World Health Organization grading of disability

Grade	Hands and feet	Eyes
0	No anesthesia, no visible deformity or damage	No eye problems due to leprosy; no evidence of visual loss
1	Anesthesia present, but no visible deformity or damage	Eye problems due to leprosy present, but vision not severely affected as a result (vision 6/60 or better; can count fingers at 6 m)
2	Visible deformity or damage present	Severe visual impairment (vision worse than 6/60; unable to count fingers at 6 m)

Source: WHO, 1988 [23]. Reproduced with permission of WHO.

potentially both sensitive and specific, although relatively expensive and impractical for use in the field [31].

### Aims of treatment

Treatment is aimed at:

- eliminating *M. leprae*;
- reducing reactions and relapse;
- preventing disabilities.

### Relevant outcomes

- Clinical outcomes:
  - percentage of patients with marked clinical improvement;
  - percentage of patients completely cured;
  - percentage of patients with treatment failure
  - percentage of patients with type I reaction;
  - percentage of patients with type II reaction;
  - percentage of patients relapsed.
- Bactericidal activity:
  - bacterial index (BI);
  - morphological index (MI);
  - mouse footpad test for *M. leprae*.
- Histopathological assessment:
  - percentage of patients with inactive leprosy.

### Methods of search

Randomized controlled trials (RCTs) dating back to 1966 were located by searching Medline, Embase, the Scientific Citation Index, and the Cochrane Library. The main search terms were RCT(s) or clinical trial(s); leprosy or lepra reactions or ENL. A Medical Subject Headings (MeSH) search was conducted if possible; otherwise a keyword search was used. References in original and review articles were reviewed and any RCTs missed from the electronic search were included. Only English-language trials were assessed.

### Questions

Because almost all RCTs on leprosy have been performed in endemic areas, care must be taken in extrapolating the results to developed countries with a low risk for leprosy.

### Is multidrug therapy more effective than monotherapy in terms of clinical outcomes and bactericidal activity?

#### Efficacy

No systematic reviews were found. Five RCTs were identified. Dietrich *et al.* compared two MDT therapy regimens with dapsone monotherapy [32]. A total of 307 patients with lepromatous leprosy and borderline lepromatous leprosy were randomly allocated to dapsone monotherapy, dapsone–rifampin, or dapsone–prothionamide–isoniazid–rifampin. The patients were treated once daily for 3 years and followed up for 5 years. Clinical improvement, regression of the disease, and bactericidal activity were measured. The results showed that dapsone monotherapy was associated with the same frequency of clinical improvement as both combinations at the end of the 5-year observation period, but with slightly slower regression. The trial did not find any statistical difference in the clearance of bacteria between the monotherapy and either combination. There was no difference in the type or frequency of reactions, but three relapses were observed with dapsone monotherapy. Ji *et al.* compared the efficacy of the combination of ofloxacin

400 mg, dapsone 100 mg, and clofazimine 300 mg daily with ofloxacin (400 mg and 800 mg) daily alone for 56 days [33]. The results showed that all of the treatment regimens were associated with remarkable clinical improvements. Marked improvements were seen in five of eight, six of eight, and six of eight cases for the combination, ofloxacin 400 mg, and ofloxacin 800 mg, respectively. The mouse footpad test showed that all three treatments led to more than 99% *M. leprae* organism clearance. There were no statistically significant differences in clinical improvement and bactericidal activity (BI and MI) between the groups. However, three ENL reactions were seen in the combination group.

Four RCTs were undertaken to compare the risk of reaction between MDT and monotherapy. Table 49.2 summarizes the results for relative risk between the two treatments [9,33–35].

Only one trial showed a significantly lower risk of type I reaction with MDT in PB leprosy [9]. The relative risk between MDT and the monotherapy was 0.12 (95% confidence interval [CI], 0.04–0.35). The number needed to harm was –6 (95% CI, –4 to –16), indicating that one in six patients would be protected from type I reactions when treated with MDT in comparison with the multiple-dose regimen of rifampicin monotherapy. Nevertheless, single-dose rifampicin (SDR) monotherapy had no more risk of the reaction than MDT.

### Drawbacks

Apart from reaction and relapse, none of the trials reported adverse drug events separately for the various treatment regimens, providing no comparative values for harms with these treatments.

### Comment

Except for two studies [9,32], all of the other trials are underpowered. Although Dietrich *et al.* indicated a rapid regression of the disease with MDT at the early stage of the treatment (6 months), there was no more benefit at the end point of 5 years with this regimen [32]. MDT was superior to multidose monotherapy in reducing type I reactions in PB leprosy [9]. However, the evidence is sparse, and the benefit of MDT disappears in comparison with SDR. As the trials differ with regard to the treatment regimens used and their duration, pooling is not possible. In addition, there are no RCTs comparing the standard WHO-MDT with dapsone monotherapy. Whether MDT is more beneficial than monotherapy has yet to be established.

### Implications for clinical practice

MDT may be useful to speed up clinical improvement and reduce type I reactions.

### Is single-dose multidrug therapy – such as 600 mg rifampicin, 400 mg ofloxacin and 100 mg minocycline – as effective as the standard World Health Organization multidrug therapy for paucibacillary leprosy in clinical outcomes?

#### Efficacy

No systematic reviews were identified. Three randomized controlled trials compared single-dose 600 mg rifampicin, 400 mg ofloxacin and 100 mg minocycline (ROM) with WHO-MDT in the treatment of PB leprosy, one for a single lesion, another for two or three lesions, and yet another for two to five skin lesions [36–38]. All the trials were double blinded. The patients were followed up for 18 months in two trials, and for 36–48 months (1082/1526) in the other. The percentages of patients with marked clinical improve-



**Table 49.2** RCTs of MDT versus monotherapy.

Trial	MDT	Monotherapy	Follow-up	Risk of reaction	MDT mono	RR (95%CI)
<i>Type I reaction</i>						
Groenen (1986) [9] (PB)	RMP 1500mg 1× + DDS 100mg od, 1y	RMP 40mg/kg 1×	>1y	4/184	5/92	0.40 (0.11–1.45)
	RMP 900mg 1/wk, 10wk			4/184	11/59	0.12 (0.04–0.35)*
Jamet (1992) [30] (MB)	CLO 50mg od + CLO 300mg 1/m, 6m	CLO 600mg 1/m, 6m	6m	2/16	1/13	1.62 (0.16–15.99)
	CLO 1200mg 1/m, 6m			2/16	7/16	0.29 (0.07–1.17)
Ji (1994) [29] (MB)	OFL 400mg od + DDS 100mg od + CLO 300mg 1/m + CLO 50mg od, 2m	OFL 400mg od, 2m	2m	0/8	0/8	1.00 (0.02–45.13)
		OFL 800mg od, 2m	2m	0/8	0/8	1.00 (0.02–45.13)
Ji (1993) [31] (MB)	MIN 100mg od + CLT 500mg od, 2m	MIN 100mg od, 2m	2m	0/12	0/11	0.92 (0.02–42.98)
		CLT 500mg od, 2m		0/12	0/12	1.00 (0.02–46.71)
<i>Erythema nodosum leprosum</i>						
Ji (1994) [29] (MB)	OFL 400mg od + DDS 100mg od + CLO 300mg 1/m + CLO 50mg od, 2m	OFL 400mg od, 2m	2m	3/8	0/8	7.00 (0.42–116.91)
		OFL 800mg od, 2m		3/8	0/8	7.00 (0.42–116.91)
Ji (1993) [31] (MB)	MIN 100mg od + CLT 500mg od, 2m	MIN 100mg od, 2m	2m	3/12	1/11	2.75 (0.33–22.69)
		CLT 500mg od, 2m		3/12	1/12	3.00 (0.36–24.92)

\*  $P < 0.01$ .

1/m, once per month; 1/wk, once per week; 1×, single dose; CI, confidence interval; CLO, clofazimine; CLT, clarithromycin; DDS, dapsone; m, month; MB, multibacillary leprosy; MDT, multidrug therapy; MIN, minocycline; od, once daily; OFL, ofloxacin; PB, paucibacillary leprosy; RMP, rifampicin; RR, relative risk; y, year.

**Table 49.3** RCTs comparing single-dose ROM and World Health Organization MDT in the treatment of PB leprosy.

First author, ref.	Design	Lesions	Follow-up (months)	Marked clinical improvement		
				Single ROM	WHO MDT	RR (95% CI)
Babu (1997) [36]	DB-P	1	18	361/697	392/684	0.90 (0.82–0.995)*
Deenabandhu (2001) [37]	DB-P	2–3	18	48/104	55/103	0.86 (0.66–1.14)
Manickam (2012) [38]	DB-P	2–5	36	485/674**	494/685**	3.2 (1.6–7.2), mid- $P$ exact, 0.001**
			48 (1082/1526)	353/468***	375/477***	2.1 (0.9–5.2), mid- $P$ exact, 0.073***

\*  $P < 0.05$ ; \*\* 36 months follow-up, complete clearance; \*\*\* 48 months follow-up, complete clearance.

DB-P, double-blind parallel; RR, rate ratio; 95% CI, 95% confidence interval; RR of relapse.

ment were slightly in favor of the WHO-MDT for a single lesion of PB leprosy. The rate ratio was 0.90, with a 95% CI of 0.82–0.995 ( $P < 0.05$ ) (Table 49.3) [36,37,39].

The number needed to treat was –18 (95% CI, –9 to –367), indicating that 1 in 18 patients will obtain marked clinical improvement when treated with WHO-MDT in comparison with single-dose ROM. However, this benefit was not seen in multiple lesions of PB leprosy (Table 49.3).

Similar results were obtained for the percentage of patients with complete cure (lesion disappearance), with the single-dose ROM regimen showing a lower rate of complete cures than the WHO-MDT regimen in patients with single-lesion PB leprosy

(relative risk [RR], 0.86; 95% CI, 0.77–0.95;  $P < 0.01$ ). However, there were no differences in the percentage of patients with treatment failure (no clinical improvement) between the two regimens in patients with single and multiple lesions. The pooled relative risk in the first two RCTs was 0.98, with a 95% CI of 0.41–2.34 ( $P > 0.05$ ). In the third trial, which took into account patients with two to five skin lesions showing complete clearance, the result at 36 months of posttreatment follow-up was similar in both the arms (72% in ROM compared with 72.1% in WHO-PB-MDT; mid- $P$  exact 0.95) [38]. At the end of 48 months of posttreatment follow-up there was a further increase in complete clearance of lesions with the proportion remaining similar (75% vs 79%; ROM vs WHO-PB-MDT;

mid-*P* exact 0.25). The mean clinical scores were also declining in a similar way. The mean clinical scores (SD) at the baseline were 13.6 (5.4) versus 13.8 (5.3) compared with 2.2 (3.5) versus 2.1 (3.4) at the end of 48 months in ROM and WHO-PB-MDT arms, respectively. However, there was a higher relapse rate among those treated with ROM (3.8%) as compared with WHO-PB-MDT (1.2%). The difference was statistically highly significant at 36 months of follow-up ( $P = 0.001$ ) (Table 49.3). At 48 months, the difference was not that significant ( $P = 0.07$ ). It was observed that 20 of the 29 relapses with ROM occurred within 18 months and the remaining nine within 36 months of completion of treatment. In the additional 12 months of follow-up, no relapses occurred in 1082 patients [38].

### Drawbacks

Gastrointestinal and allergic adverse drug events were assessed in all trials. There were no statistically significant differences between the single-dose regimen and the WHO-MDT regimen. The pooled relative risk in the first two trials was 0.48 (95% CI, 0.15–1.56). In the trial, 10 suspected adverse drug reactions were reported. Eight of 10 among these were observed in the WHO-PB-MDT arm. Though statistically not significant, the occurrence of more drug reactions in the WHO-PB-MDT arm was of clinical significance [38].

Reaction and neuritis were also compared, and nonstatistical differences were obtained. The relative risks in the first two trials for these between the single-dose treatment and WHO-MDT were 2.66 (95% CI, 0.78–9.13) and 3.02 (95% CI, 0.31–28.97), respectively. In the third trial, one T1R in each of the arms was observed.

### Comment

The three RCTs that compared single-dose ROM with WHO-MDT were generally of good quality. The first and the third trials were well powered, with drop-out rates of 6% and 11%, respectively. The results show that clinical improvement (the percentage of patients with marked improvement or complete cure) is slightly in favor of the WHO-MDT regimen in the RCT with a single lesion of PB leprosy, but not with two or three lesions. There was hardly any difference of efficacy in the larger RCT with PB leprosy having two to five lesions. There are no differences in the other outcomes, such as treatment failure and reaction. Regarding side effects, there is no statistical difference between ROM and WHO-PB-MDT, but the latter demonstrated the occurrence of adverse drug reactions that would be clinically significant. The RCT with the longest follow-up indicated that ROM had a significantly higher relapse rate, the relapses having been essentially observed in the first 2 years of follow-up.

### Implications for clinical practice

The clinical efficacy of single-dose ROM in PB leprosy with up to five skin lesions is comparable to WHO-PB-MDT in clearing the lesions. However, ROM has a significantly greater tendency of causing relapse. If single-dose ROM is to be incorporated as a standard treatment regimen, active surveillance of the patients for at least 2 years has to be mandatory. This would require training of treating physicians in clinical evaluation of leprosy patients to detect reactions, relapses, and treatment failures, and it also brings in the question of patient compliance beyond the period of active treatment. Such close surveillance would thus be beyond the logistic capabilities of most leprosy programs. Therefore, single-dose ROM is not practically implementable at present, keeping the field

conditions in consideration. Minor modifications in ROM do not help in improving the clinical outcome, as an RCT assessing the effect of adding clarithromycin to ROM in the treatment of single-lesion PB leprosy found that the addition did not significantly improve the efficacy as measured in terms of cure rates and relapse rates [40].

For the patient in the clinical scenario described at the beginning of this chapter, single-dose ROM would not be suitable if he had more than five lesions at presentation. Even if the patient had up to five skin lesions, he would have to undertake submitting himself to close active surveillance for a period of at least 2 years if he wanted to be treated by single-dose ROM.

## Is 6 months of uniform multidrug therapy as safe and effective as 12 months of World Health Organization multidrug therapy in multibacillary leprosy?

### Efficacy

No systemic reviews were found. Two trials were identified. One was an open comparative trial between WHO-MDT (12 months) and uniform MDT (U-MDT, 6 months) in all types of leprosy over 24 months of observation [41]. Out of the 127 patients included, 64 patients (MB leprosy: 32/64) could be followed up regularly, and 44 of them were also assessed at 24 months of the study. The MB WHO-MDT and U-MDT groups were comprised of 22 and 10 patients, respectively. As per clinical improvement grading, good responses in the WHO-MDT group were 36%, 45%, and 77% at 12 months, 18 months, and 24 months of study, respectively, whereas the U-MDT group did not have a single good response at 12 and 18 months, with the poor responses being 50%, 67%, and 75% at 12 months, 18 months, and 24 months, respectively. These differences between the groups were statistically significant at all time intervals (at 12 months,  $P = 0.0465$ ; at 18 months,  $P = 0.0014$ ; at 24 months,  $P = 0.0064$ ). Histopathological assessment showed a higher percentage of good responses in the WHO-MDT group (100%) compared with U-MDT (50%) at 18 months.

The other trial was an open-label RCT comparing WHO-MDT with U-MDT, the primary outcome measure being the association of the treatment duration with the frequency of reactions among MB patients [42]. The reaction frequency in time was analyzed using the Kaplan–Meier survival function comparing the two groups and stratified by  $BI < 3$  and  $BI \geq 3$ . Those on UMDT (120/316) had more reactions than those on WHO-MDT (90/280). The biggest difference in the free-of-reaction proportion as a function of time was found around 1 year (difference of 11.9% at 1.15 years). The gap closed down around 2 years. Those with  $BI \geq 3$  had a higher frequency of first reaction than those with  $BI < 3$  throughout the observation time. The incidence of recurrent reaction presented a positive association with  $BI \geq 3$  and with U-MDT. The interaction term showed statistical significance, meaning that the simultaneous influence of U-MDT and  $BI \geq 3$  was less than the sum of the effect of each of these variables. There was a very strong association between the occurrence of T2R and  $BI \geq 3$ : an odds ratio of 11. Surprisingly, the difference in reaction frequency between treatment groups was more relevant among those with a low BI than those with a high BI.

### Drawbacks

Other than T1R and T2R, dapsone syndrome ( $n = 1$ ), acute generalized exanthematous pustulosis to dapsone ( $n = 1$ ), and clofazimine pigmentation ( $n = 11$ ) were recorded in one trial [41].

## Comment

The first study was a quasi-randomized (alternate allocation) open study with inadequate statistical power. The histopathological comparison should be treated with particular caution as the number of biopsy samples was so small that statistical methods could not be applied. Still, it has been included here because of the paucity of direct comparative studies between 6-month and 12-month MDT. The main problem in evaluating any new treatment regimen in leprosy is that there are no good and reliable data available for the current 12-month regimen. No RCT supports the reduction of treatment duration to 12 months for MB patients [42]. Only one multicentric, initially double-blinded clinical trial in 189 MB leprosy cases exist where, after 12 years of initiation of treatment, not a single case of long-term relapse was found in the 24-month MDT group, and a relapse rate of 3% (1/36) was recorded in the 12-month WHO-MDT group [43]. A hospital-based retrospective data analysis carried out in eastern India a decade after the commencement of the 12-month WHO-MDT showed that significant transmission of leprosy has been going on in the community, as evidenced by a significantly higher proportion of PB disease compared with MB leprosy [44].

In this context, the observation that MB patients on U-MDT showed a significantly poor response at all periods of clinical assessment at 12, 18, and 24 months compared with the patients on WHO-MDT [41] is relevant. Similarly relevant is the finding of the RCT [42] that shows that although the risk of first reaction converges 2 years after the beginning of treatment, the Kaplan–Meier curves separate when the U-MDT ends and the WHO-MDT group patients are still taking their drugs. It is also relevant that the same trial found that the incidence of recurrent reaction was associated with treatment duration and initial BI.

## Implications for clinical practice

There is no evidence that 6-month U-MDT is as efficacious or safe as the current 12-month WHO-MDT with regard to MB leprosy. Hence, there is no rationale to implement 6-month U-MDT only on operational grounds.

## Does a daily 4-week ofloxacin–rifampicin regimen have similar long-term relapse rates as the standard World Health Organization multidrug therapy in paucibacillary and multibacillary leprosy?

### Efficacy

No systematic review was identified. Three double-blind RCTs were identified [43,45,46]. Two of them compared the long-term relapse rates of ofloxacin–rifampicin with the WHO-MDT in MB leprosy [43,45] and one [46] compared the same in PB leprosy. The RCTs were too heterogeneous to combine in a statistical analysis.

In one of the multicenter trials [43], carried out in the Philippines, the relapse rates in 189 MB leprosy patients were treated with four different regimens and were followed up for as many as 12 years after the initiation of treatment. Treatment regimens included 1-year WHO-MDT, 2-year WHO-MDT, 1-month daily ofloxacin–rifampicin, and 1-year WHO-MDT plus initial 1-month daily ofloxacin–rifampicin. Relapse rates after 9 and 12 years from the initiation of therapy in the three regimens that included WHO-MDT were 0–3%, whereas relapses occurred in those treated with the 1-month regimen alone at a significantly greater rate ( $P < 0.05$ ): 11% at 9 years and 25% at 12 years. Relapses occurred late, beginning at 5 years after the initiation of therapy, and were confined to

those patients who were histopathologically borderline lepromatous and polar lepromatous having a high bacterial burden. No difference in the relapse rates (3% each at 12 years) for the two regimens employing WHO-MDT for 1 year (alone and with initial 1 month of daily ofloxacin–rifampicin) means there is no additional benefit of adding 1-month daily ofloxacin–rifampicin to the existing WHO-MDT regimen in MB leprosy. Though there was no statistically significant difference with 1-year WHO-MDT, it is noteworthy that only the 2-year WHO-MDT study population showed zero relapse at 2 years.

In another multicentric double-blind RCT with 198 MB patients [45], done in Brazil, employing four identical regimens with a shorter follow-up period (7 years after release from treatment), relapse occurred in those treated with 1-month regimen alone at a significantly higher rate ( $P < 0.001$ ): 38.8% (19/49; 95% CI, 25.5–53.3). In the other three regimens that included WHO-MDT it ranged from 0 to 5%. (in the 2-year WHO-MDT, there was zero relapse ( $n = 24$ ); in the 1-year WHO-MDT, relapse rate was 4.3% (2/46; 95% CI, 0.8–16.0); and in the group treated with 1-year WHO-MDT plus 1-month initial daily ofloxacin–rifampicin the relapse rate was 5% (2/40; 95% CI, 0.3–18.2). All relapses occurred in patients who were initially BL or LL and had a baseline average BI of  $4.2 \pm 0.84$ . These results indicate close correlation between relapse and high initial BI. These results, in spite of a much shorter follow-up period compared with the Filipino study, mirror those results demonstrating that 1 month of rifampicin and ofloxacin daily was insufficient in the treatment of MB leprosy.

In another double-blind, placebo-controlled, randomized trial carried out in the Philippines [46], 124 patients of PB leprosy were enrolled. Of them, 66 received the standard 6-month WHO-MDT regimen, whereas 58 received 28 daily supervised doses of rifampicin 600 mg + ofloxacin 400 mg, plus 5 months of placebo. Patients enrolled in the WHO-MDT group had a mean follow-up of 11.3 years with two late relapses at 8 and 12 years. Among those enrolled in the ofloxacin group, a mean follow-up of 10.8 years showed one early relapse at 3 years after treatment completion. The results show that the 4-week ofloxacin regimen was as safe and effective as the 6-month WHO-MDT regimen in PB leprosy.

### Drawbacks

The trial with PB leprosy [46] recorded mild reversal reaction in 4.5% (3/66) in the WHO-MDT group and 12% (7/58) reversal reactions in the rifampicin–ofloxacin group, two of which were considered to be moderate to severe. One patient in the ofloxacin group developed grade 2 deformity after treatment. One patient in the same group complained of occasional epigastric pain (not requiring cessation of treatment) towards the later part of treatment. In the Brazil trial on MB leprosy [45], among 183 patients who completed the course of treatment, three patients were decoded due to severe side-effects, including one on ofloxacin–rifampicin. Incidence of reversal reactions, if any, was not mentioned. There was no mention of any adverse effects in one study [43]. Overall, the incidence of side-effects was low, except that of reversal reactions in PB leprosy patients on ofloxacin–rifampicin.

### Comment

The three RCTs were well designed. The two trials on MB leprosy found that the relapse rate on the 4-week daily regimen of ofloxacin–rifampicin was significantly higher than three other regimens that included 1-year WHO-MDT, 1-year WHO-MDT plus 1-month initial daily ofloxacin–rifampicin, and 2-year WHO-MDT. It was

also found that the addition of 1 month of daily ofloxacin–rifampicin to 1-year WHO-MDT did not increase in its efficacy, as evidenced by the relapse rate – while in one trial the relapse rate of the combined regimen was, in fact, higher than the WHO-MDT alone (5% vs 4.3%), but not significantly so, in the other trial the rate was exactly the same (3%).

As suggested earlier [47], a short incubation period for relapse could have correlation with drug resistance. The short incubation period (2.5 years follow-up) for relapse in the case of ofloxacin resistance seems to suggest the possibility of relapse due to drug resistance [45].

Another important observation is the zero relapse with 2-year MDT, though this could be due to the small cohorts (9 and 24, respectively at the end of 12 years and 7 years) and insufficient follow-up period.

In PB leprosy, the 4-week ofloxacin regimen was found to be as safe and effective as the PB WHO-MDT. However, the early relapse in the ofloxacin regimen gives rise to the possibility that the short regimen might be inadequate in a small proportion of PB cases with a higher bacillary load. This possibility renders the applicability of the ofloxacin regimen even in PB leprosy doubtful, as it is very difficult to determine the treatment in the field on the basis of bacillary load.

### Implications for clinical practice

A 4-week ofloxacin–rifampicin daily regimen is not suitable for treating MB leprosy on account of a high relapse rate in comparison with the current 1-year WHO-MDT. The same regimen was found to be as safe and effective as the 6-month PB WHO-MDT. But the occurrence of early relapse in cases of higher bacillary load in PB leprosy with ofloxacin means that it is difficult to apply this regimen in the field, particularly in the endemic areas in the developing world.

### Is there any efficacious treatment for erythema nodosum leprosum?

#### Efficacy

One systematic review was identified [48]. It included 13 randomized trials with a total of 445 participants. The interventions included were: betamethasone (single trial), thalidomide (five trials), pentoxifylline (single trial), clofazimine (three trials), indomethacin (two trials), and levamisole (single trial). Treatment with thalidomide showed a significant remission of skin lesions compared with acetylsalicylic acid (aspirin) (RR, 2.43; 95% CI, 1.28–4.59 – single trial, 92 participants). Clofazimine treatment was superior to prednisolone (more treatment successes; RR, 3.67; 95% CI, 1.36–9.91 – single trial, 24 participants), and thalidomide (fewer recurrences; RR, 0.08; 95% CI, 0.01–0.06 – single trial, 72 participants). There was no significant benefit for intravenous betamethasone compared with dextrose (single trial, 10 participants), pentoxifylline compared with thalidomide (single trial, 44 participants), indomethacin compared with prednisolone, aspirin, or chloroquine (two trials, 80 participants), or levamisole compared with placebo (single trial, 12 participants).

#### Drawbacks

Twenty cases of drowsiness, eight cases of dizziness, and seven cases of nausea were seen with thalidomide treatment among 85 patients, whereas none was found with placebo [49]. Mild to moderate adverse events were significantly lower in participants taking 100 mg thalidomide compared with 300 mg thalidomide daily (RR,

0.46; 95% CI, 0.23–0.93;  $n = 22$ ) [50]. Significantly more minor adverse events were reported in participants taking clofazimine compared with prednisolone (RR, 0.46; 95% CI 1.10–3.35;  $n = 24$ ) [51].

### Comment

The quality of the trials was generally poor in relation to the Consolidated Standards of Reporting Trials (CONSORT) statement [52]. No results could be pooled owing to the interventions being so heterogeneous. There was some benefit for thalidomide and clofazimine, but generally there was no clear evidence of benefit for interventions in the management of ENL. However, this does not mean that they do not work, because the trials were small and poorly reported. However, it must be emphasized that because of its well-known teratogenicity, thalidomide should be given only to males and postmenopausal females. Women of childbearing age should never be given thalidomide. Thalidomide is also known to be associated with irreversible nerve damage. It must, therefore, be administered under the strictest possible supervision.

It is noteworthy that the results of a double-blind trial strongly support the beneficial effects of pentoxifylline in treating ENL [53]. Clinical evaluations carried out at the end of 30 days of treatment clearly indicated that the overall response to thalidomide was significantly better than the response to pentoxifylline ( $P = 0.02$ ;  $n = 44$ ). However, the results suggested that pentoxifylline could represent a good alternative treatment for ENL patients for whom thalidomide is contraindicated.

A randomized comparative trial was published recently comparing thalidomide and prednisolone in moderate to severe ENL [54]. Sixty adult MB patients with a histologically confirmed diagnosis of moderate to severe ENL were randomly allocated to two groups with similar baseline characteristics. Thalidomide had a very significantly superior efficacy across all clinical outcome parameters; namely, time taken for resolution of cutaneous lesions as well as constitutional symptoms, mean period of remission, and number of relapses ( $P < 0.0001$ ). Adverse events were more commonly noted in the prednisolone group. However, two patients had to be taken out of the thalidomide group, one on account of leukocytoclastic vasculitis and the other because of gastrointestinal symptoms.

### Implications for clinical practice

Thalidomide may be useful for improving the clinical symptoms of ENL, but owing to its well-known teratogenicity and neurotoxicity, care must be taken when it is being used for ENL. Current evidence would support the use of thalidomide in moderate to severe ENL, and clofazimine in mild ENL. Pentoxifylline can be employed where thalidomide is contraindicated. There is no ground for preferring the use of corticosteroids in ENL with respect to the above-mentioned interventions.

### In patients with leprosy, does steroid treatment improve nerve function impairment?

#### Efficacy

One systematic review was identified [55]. Three RCTs involving 513 participants were included. The interventions and outcomes were too heterogeneous to be entered in a meta-analysis. Risk of bias was generally low in the three RCTs. None of the trials found a significant difference in improved nerve function between treatment and control groups 12 months after start of treatment. Two trials compared prednisolone with placebo. One trial with 84 par-



ticipants treated mild sensory impairment of less than 6 months' duration, and the other trial, which had 95 participants, treated NFI of 6–24 months' duration. After 12 months of starting treatment, there was no significant difference in nerve function improvement between subjects treated with prednisolone or with placebo. The third trial compared three corticosteroid regimens for severe T1R in 334 participants. The results showed significant benefit of a 5-month steroid regimen over a 3-month regimen. After 12 months, a significantly higher proportion of individuals on the 3-month course of prednisolone required extra corticosteroids, a measure of poor outcome, compared with the groups with a high-dose and low-dose regimen of 5 months' duration. The main objective of this trial was to investigate failure to respond to the given corticosteroid regimen. Unfortunately, the effect of different corticosteroid regimens on nerve function improvement was not evaluated, which makes this trial unsuitable for comparison with other included trials.

### Drawbacks

The adverse effects of long-term steroid use are well known and include fluid retention, weight gain, redistribution of body fat, osteoporosis, muscle wasting, thinning of skin, and psychological effects, including irritability and depression. However, the occurrence of adverse effects was not significantly higher in the corticosteroid group compared with the placebo group (RR, 1.47; 95% CI, 0.35–6.24) [55]. While only two trials, which were limited in size and power, reported adverse effects, the evidence was inconclusive. Diabetes and peptic or infected ulcer were sometimes reported as serious adverse events in the placebo-controlled trials, but not significantly more often in the corticosteroid than in the placebo groups. Therefore, the occurrence of these major adverse events should not be considered a contraindication for corticosteroid treatment.

### Comment

Corticosteroids are used for treating acute nerve damage in leprosy, but evidence from two RCTs, treating either long-standing or mild NFI, did not show a significant long-term effect. A third trial showed significant benefit of a 5-month steroid regimen over a 3-month regimen. Standard corticosteroid regimens are not significantly more harmful than placebo treatment, despite known adverse effects of corticosteroids.

A more recent RCT of oral steroids for ulnar neuropathy in 21 patients with T1R ( $n = 12$ ) and T2R ( $n = 9$ ) showed that during the first month higher doses of steroids produced better results in both reactions, but earlier treatment with a lower dose was as effective [56]. The outcome was based on clinical score as well as neurophysiological evaluation. The results from this cohort of leprosy patients in reactional states are very relevant because it is known that while peripheral nerve damage can be demonstrated in almost all the patients with leprosy, a reaction episode significantly increases the severity of the problem in terms of extent of nerve damage and visible grade 2 disability [57].

In another recent RCT, 42 individuals with T1R were randomized to receive methylprednisolone followed by oral prednisolone ( $n = 20$ ) or oral prednisolone alone ( $n = 22$ ) [58]. There were no significant differences in the rate of occurrence of adverse events or clinical improvement at the completion of the study. However, individuals treated with methylprednisolone were less likely than those treated with prednisolone alone to experience deterioration in sensory function between day 29 and day 113 of

the study. The study also demonstrated that 50% of individuals with T1R and/or NFI required additional prednisolone despite treatment with 16 weeks of corticosteroids. Thus, this study also lends further support to the use of more prolonged courses of corticosteroid to treat NFI in T1R. However, the results of this small study should be used with caution. The study was underpowered and, thus, limited the ability to detect significant differences of less than 30% between the groups.

### Implications for clinical practice

On the basis of the results of these studies, the patient should be informed that the routine use of steroids may only have short-term benefits. Surprisingly, despite the corticosteroids having many known adverse effects, it has been consistently found that the incidence of adverse reaction with steroids is no greater than that with placebo. More than one study has suggested that a more prolonged course of steroids would be more efficacious in improving nerve function without significantly increasing the risk of adverse effects. However, most of the studies were too small to lead to robust evidence. Studies are needed to confirm the long-term effect of using steroids.

### Does any intervention have clinically beneficial outcome in the healing of trophic ulcers in patients with leprosy?

#### Efficacy

One systematic review was retrieved [59]. Eight randomized trials with a total of 557 participants were included. The interventions and outcome measures were diverse. Although three studies that compared zinc tape with more traditional dressings found some benefit, none of these showed a statistically significant effect. One trial indicated that topical ketanserin had a better effect on wound healing than clioquinol cream or zinc paste (RR, 6.00; 95% CI, 1.45–24.75). Two trials comparing topical phenytoin and saline dressing found statistically significant effects in favor of phenytoin for healing of ulcer (standardized mean difference [SMD],  $-2.34$ ; 95% CI,  $-3.30$  to  $-1.39$ ; SMD,  $-0.79$ ; 95% CI,  $-1.20$  to  $+0.39$ ). Canvas shoes were not significantly better than PVC boots, and double rocker shoes did not promote healing significantly more than below-knee plasters.

### Drawbacks

Three studies – one on topical ketanserin versus clioquinol cream or zinc paste [60], one on topical phenytoin versus saline dressing [61], and the third study comparing zinc tape versus gauze with Eusol [62] – reported that no adverse effects of the treatment were observed, while no other included study reported adverse effects at all.

### Comment

Most of the trials were found to have poor methodological quality with a high risk of selection and detection bias [63]. Only two trials seemed to have taken measures to blind outcome assessors. In half the studies the authors did not or failed to show that the groups were comparable at baseline. Two studies clearly had such losses to follow-up that it could be detrimental to the validity of results, while another study was unclear as to how many participated in the analyses. Studies with losses of 20% or below were rated as having adequate follow-up. In fact, only one study [61] out of the eight would conform to the CONSORT guideline [52]. Overall, the

inadequate reporting of the trials could be a threat to the validity of this systematic review.

Topical ketanserin may be more effective than clioquinol cream or zinc paste and topical phenytoin may be more effective than saline dressing in ulcer healing. However, this is based on very weak evidence. For topical ketanserin, only one study tested the comparison; and for phenytoin, the summary analysis of two studies did not show a clear effect. For the other comparisons the results were equivocal. Three studies reported that no adverse effects of treatment were observed.

A recent RCT on the effect of low-level laser therapy with an indium–gallium–aluminum phosphide semiconductor laser on the healing of ulcers in 13 leprosy patients found no statistical difference with the control group who received routine wound care with sterile dressing [64].

### Implications for clinical practice

There is a lack of high quality research in the field of ulcer prevention and treatment in leprosy. Weak evidence suggests that topical ketanserin may be more effective than clioquinol cream or zinc paste, and topical phenytoin may be more effective than saline dressing in trophic ulcer healing in leprosy. Low-level laser therapy does not have any additional benefits to conventional wound care. New trials should be taken up that follow current standards for design and reporting of RCTs.

### Does decompressive surgery have any additional benefit to oral steroids in the treatment of nerve damage of less than 6 months' duration in leprosy?

#### Efficacy

One systematic review was identified [65]. Two RCTs involving 88 participants were included in the review. One trial compared the added benefit of medial epicondylectomy over corticosteroids for participants with ulnar neuritis of less than 6 months' duration [66]. The other trial compared the added benefit of longitudinal epineurotomy over corticosteroids for participants with ulnar, median, common peroneal, or posterior tibial nerve involvement of less than 6 months' duration [67]. The interventions and outcomes were too heterogeneous to be combined in a meta-analysis. After 2 years of follow-up there was only very low-quality evidence of no significant difference in nerve function improvement between participants treated with surgery plus prednisolone or with prednisolone alone.

#### Drawbacks

Adverse effects of decompressive surgery were not adequately described in any of the reports. One study [67] excluded a participant with hemorrhage during the course of the trial, but it was unclear whether this was due to the intervention. The literature reviewing decompressive surgery in leprosy often does not take adverse effects into account, but stresses the importance of having adequate techniques and instruments and competent surgeons to prevent unfavorable outcomes [68]. Complications of decompressive surgery in general may be painful scars, wound problems, hematoma, infection, and damage to nerves, arteries, or tendons [69].

#### Comment

The number of participants in both the trials was too small to allow subgroup analysis. The variability between studies and the limita-

tions in study design and sample size made it difficult to draw any robust conclusions. None of the trials found a significant improvement in improved nerve function between surgical decompression and prednisolone-only groups after a follow-up of 1 or 2 years. This result may have been biased by the selection criteria used for inclusion of patients and nerves. Only about 10% of the cases of neuritis may benefit from decompressive surgery and show improvement after surgery [65]. Not all nerves need decompression. By taking all nerves together, the results might have been misleading.

### Implications for clinical practice

Surgical decompression is used for treating nerve damage in leprosy, but the available evidence from RCTs is of very low quality and does not show any significant added benefit of surgery over steroid treatment alone. Well-designed RCTs are required to establish the effectiveness of the combination of surgery and medical management compared to medical treatment alone.

### In endemic areas, is chemoprophylaxis effective in preventing leprosy?

#### Efficacy

One recent systematic review was retrieved [70], which identified 320 references, from which seven RCTs with a total of 66 311 participants were included and evaluated. The combined results from the RCTs favored chemoprophylaxis to placebo with 2–4 years of follow-up (six RCTs; 66 107 participants; RR, 0.59; 95% CI, 0.50–0.70;  $I^2 = 0$  [ $I^2$  represents percentage total variation across studies caused by heterogeneity]). SDR (21 711 participants; RR, 0.43; 95% CI 0.28–0.67; number needed to treat, 285), dapsones once or twice weekly for at least 2 years (three RCTs; 43 137 participants; RR, 0.60; 95% CI, 0.48–0.76;  $I^2 = 0$ ), and acedapsone every 10 weeks for 7 months (two RCTs; 1259 participants; RR, 0.49; 95% CI, 0.33–0.72;  $I^2 = 0$ ) were significantly superior to placebo in preventing secondary cases of leprosy.

#### Drawbacks

Particularly with dapsones, chemoprophylaxis was often continued for several years after the index case was cured; side effects, compliance, and drug resistance would therefore be likely to cause significant long-term problems if such a strategy were to be implemented.

#### Comment

Almost all of the clinical trials that were performed in the 1960s and 1970s used dapsones alone, at a time when dapsones resistance was high. The duration of follow-up was also limited to a few years, and it is possible that chemoprophylaxis may simply delay the onset of leprosy. Most of the RCTs were judged as having an unclear risk bias. Only one RCT was found with low risk of bias [71]. The latter was a single-centre, double-blind, cluster-randomized, placebo-controlled trial, named COLEP, that was carried out among 28 092 close contacts of 1037 patients in Bangladesh. The number of contacts that were finally included who fulfilled the study requirements was 21 711. SDR or placebo was given to the participants in the second month of starting the index patient's treatment, with follow-up for 4 years. The overall reduction in incidence of leprosy using a single dose of rifampicin in the first 2 years was 57% (95% CI, 0.33–0.72). The groups did not differ between 2 and 4 years. The number needed to treat to prevent a single case of leprosy among contacts was 285 (RR, 0.43; 95% CI, 176–537). In years 3 and 4, no statistically significant difference was found between the numbers

of new cases in the groups. Thus, it was concluded that a single dose of rifampicin given to contacts of patients with newly diagnosed leprosy was effective at preventing the development of clinical leprosy at 2 years. The effect was maintained, but no significant difference was seen between the placebo and rifampicin groups beyond 2 years. However, the total impact of the intervention was still statistically significant ( $P = 0.025$ ) after 6 years and no excess cases were observed in the SDR arm at a later stage [72]. The intervention prevented leprosy in contacts that actually received SDR, but did not offer protection to members of the same contact group who did not take chemoprophylaxis. The cost-effectiveness of SDR prophylaxis was assessed in the COLEP study by calculating the incremental cost-effectiveness ratio between the standard MDT program with the additional chemoprophylaxis intervention versus the standard MDT program only [73]. It was found that chemoprophylaxis with SDR for preventing leprosy among contacts of newly diagnosed leprosy patients was cost-effective at all contact levels and thereby a cost-effective prevention strategy.

In another RCT, which was too heterogeneous to be analyzed along with the other trials, serological response to chemoprophylaxis with a single dose of ROM (among adults above 15 years) and SDR (by body weight, among children up to 15 years) among seropositive extended contacts ( $n = 300$ ) of new leprosy cases was compared with placebo by testing for immunoglobulin M antibodies using the natural trisaccharide phenyl propionate-bovine serum albumin enzyme-linked immunosorbent assay test in Myanmar [74]. The mean optical density titers before and after chemoprophylaxis were 0.24 versus 0.10 and 0.20 versus 0.09 in the treated and nontreated groups, respectively, in adults ( $P = 0.004$ ), and 0.25 versus 0.11 and 0.22 versus 0.11, respectively, in children ( $P = 0.18$ ) after 1 year. These were 0.24 versus 0.17 and 0.20 versus 0.19 ( $P = 0.0005$ ) and 0.25 versus 0.19 and 0.22 versus 0.20 respectively in children ( $P = 0.103$ ) after 2 years. The difference of mean antibody titers before and after single-dose ROM chemoprophylaxis in the treated group was significantly reduced compared with the nontreated group in adults (204 participants; mean difference, 0.06; 95% CI, 0.04–0.08) but was not significant with SDR prophylaxis in children (96 participants; mean difference, 0.04; 95% CI, 0.01–0.09).

### Implications for clinical practice

In endemic areas, chemoprophylaxis using oral dapsone or intramuscular acedapsone for household contacts may provide up to 60% protection against leprosy. SDR in contacts of newly diagnosed patients of leprosy was 57% effective at preventing the development of leprosy after 2 years. A 6-year follow-up suggested that the impact of the SDR chemoprophylaxis was still significant at that time. Chemoprophylaxis with SDR given to contacts of newly diagnosed leprosy patients is also a proven cost-effective intervention strategy at all contact levels. Single-dose ROM chemoprophylaxis in adult extended contacts of leprosy patients has shown significant serological response at 2 years of follow-up.

### Is bacille Calmette–Guérin effective in the prevention of leprosy?

#### Efficacy

A systematic review has been published with evidence from both clinical trials and observational studies [75]. Seven clinical trials (RCTs or controlled trials) were included in the meta-analysis. The risk of leprosy in the bacille Calmette–Guérin (BCG) group was significantly lower than that in the placebo group (pooled RR, 0.74;

95% CI, 0.63–0.86) (Figure 49.2). The authors also carried out a meta-analysis of 19 observational (cohort and case–control) studies. The results supported the conclusion from the clinical trials, with better statistical power and larger preventive effects (RR, 0.39; 95% CI, 0.30–0.49). A meta-analysis published later, which took into account 22 studies (six trials, two cohort studies, and 14 case–control studies), also reached similar conclusions [76].

### Drawbacks

BCG vaccine is not free from adverse effects. Fatal disseminated BCG infection has been reported among people with HIV infection [77]. As with other vaccines, the risk of using BCG will need to be assessed against its benefits.

### Comment

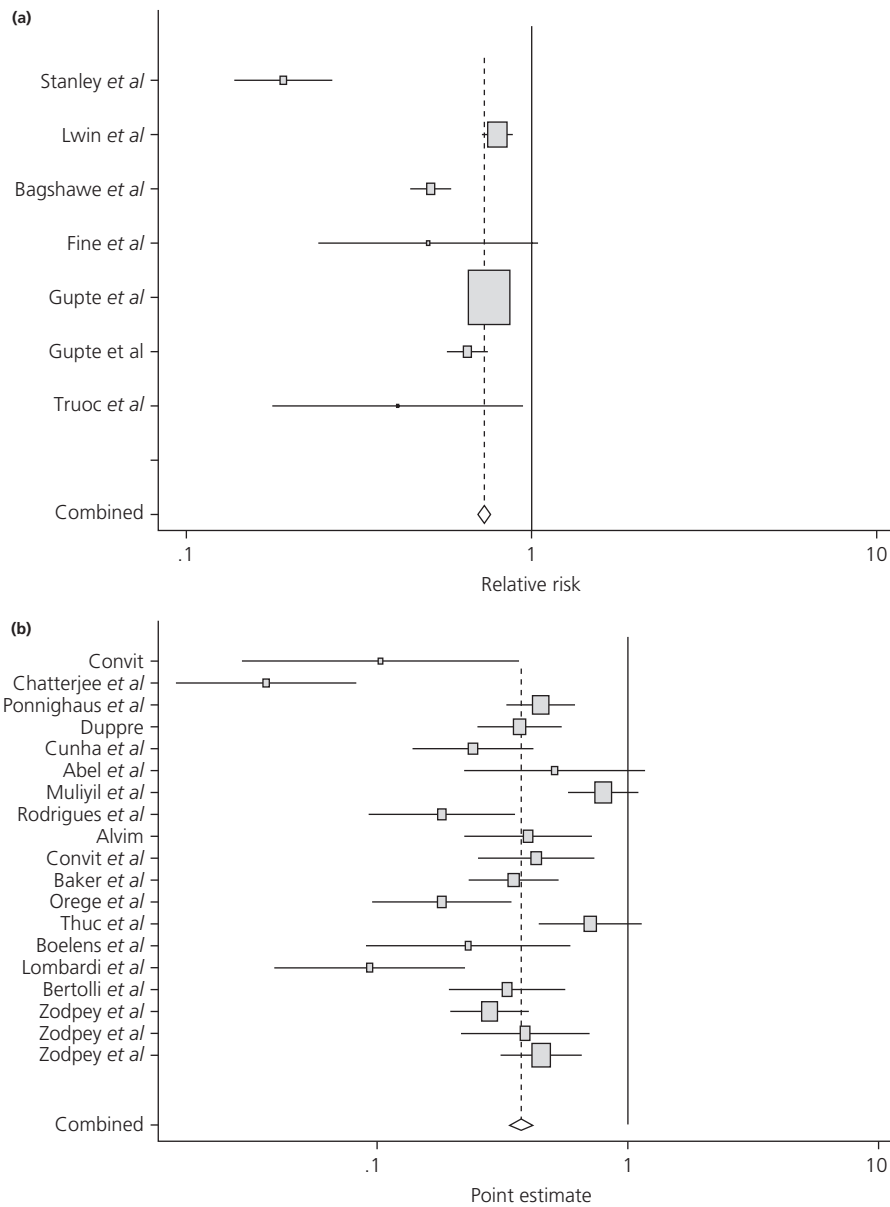
The BCG vaccine contains a mycobacterium that is closely related to *M. leprae* and is recommended by the WHO's Expanded Programme on Immunization for protection against tuberculosis. It is routinely used to vaccinate children in countries in which leprosy continues to be a public health problem, and it is currently recommended for the household contacts of leprosy patients. It has been well investigated in RCTs, cohort studies, and case–control studies. The evidence from different studies uniformly supports the use of BCG to prevent leprosy, although the size of the effect in different studies varies, possibly due to differences in the study designs and populations involved. However, the utility of repeat or booster BCG vaccinations is still unclear. In a cluster randomized community trial in Brazil, with 6 years and 8 months of follow-up, 99 770 school children with neonatal BCG were inducted, among whom 42 662 were in the revaccination arm [78]. The incidence rate ratio of leprosy in the intervention over the control arm within the follow-up, controlled for potential confounders and adjusted for clustering, was 0.99 (95% CI, 0.68–1.45). Thus, there was no evidence of protection conferred by the second dose of BCG vaccination in school children against leprosy during the trial follow-up. In another interesting offshoot of the COLEP trial mentioned earlier, both univariate and multivariate analysis of the trial data showed that a protective effect was seen in contacts that received either SDR or BCG, compared with contacts with no intervention (BCG-adjusted protective effect was 57% (95% CI, 24–75%); for SDR 58% (95% CI, 30–74%)) [79]. In contacts receiving both the interventions, the protective effect was 80% (95% CI, 50–92%). Thus, there is a demonstrated additive effect of immunoprophylaxis by routine infancy BCG vaccination and chemoprophylaxis with SDR given to close contacts of newly diagnosed leprosy patients.

### Implication of clinical practice

Given its protective effects and easy availability, BCG vaccination is warranted in regions in which leprosy continues to be a public health problem and in household contacts who are at greater risk of acquiring the infection. However, there is no evidence that BCG revaccination would offer additional protection. Instead, SDR has a demonstrated additive effect to BCG vaccination in infancy in providing protection in close contacts of newly diagnosed leprosy patients.

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**Figure 49.2** Meta-analyses of clinical trials (a) and observational studies (b) on the role of BCG in the prevention of leprosy. The rectangles represent the point estimates for each study, the size of the rectangle represents the weight allocated to each study, and the horizontal lines represent the 95% confidence intervals. The diamond and vertical broken line represent the summary estimate and the size of the diamond represents the 95% confidence intervals of the summary estimate. The solid vertical line is the null value. (Reproduced with permission from Setia *et al.*, 2006 [75]. Reproduced with permission from Elsevier.)



## Key points

- Although chemotherapy is the main treatment for leprosy, there is a lack of robust placebo-controlled trials.
- MDT may be useful to speed up clinical improvement, but may offer no greater benefit than single agents in bacterial clearance.
- WHO-MDT is superior to the single-dose regimen of ROM with regard to clinical improvement and rate of relapse in MB leprosy.
- There is no evidence that 6-month U-MDT is as efficacious or safe as the current 12-month WHO-MDT with regard to MB leprosy.
- Current evidence would support the use of thalidomide in moderate to severe ENL. However, it must not be used in women of childbearing age and it has to be monitored carefully because of its neuropathic side effects.
- There is no ground for preferring the use of corticosteroids in ENL over other effective interventions like thalidomide or clofazimine.
- Routine use of steroids may only have short-term benefits in improving nerve function impairment in leprosy.
- Weak evidence suggests that topical ketanserin may be more effective than clioquinol cream or zinc paste, and topical phenytoin may be more effective than saline dressing in trophic ulcer healing in leprosy.
- Surgical decompression is used for treating nerve damage in leprosy, but the available evidence from RCTs does not show any significant added benefit of surgery over steroid treatment alone.
- Chemoprophylaxis with SDR given to contacts of newly diagnosed leprosy patients is efficacious and also a proven cost-effective intervention strategy at all contact levels.
- BCG is effective in preventing leprosy. It is recommended to protect people from the infection in endemic areas or among household contacts. However, revaccination with BCG does not afford additional protection.
- Care has to be taken when extrapolating the evidence to developed countries, as most of the studies have been carried out in developing countries, and in regions where leprosy is endemic.

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# Cutaneous leishmaniasis

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## Background

### Definition

Leishmaniasis is a group of diseases caused by infection with protozoan parasites called *Leishmania*, transmitted by bites from sandflies infected with the microorganisms [1,2]. The parasite may be transmitted from person to person or from a range of animals to humans. Leishmaniasis is globally a poverty-related disease and is associated with war, malnutrition, displacement, poor housing, illiteracy, and gender discrimination. Leishmaniasis is also linked to environmental changes and migration to endemic areas.

There are several clinical presentation forms, which are associated with a broad range of signs, symptoms, and degrees of severity. Cutaneous leishmaniasis (CL) is the most common form of presentation. After an incubation period of 1–12 weeks, a papule develops at the site of the insect bite. The papule grows and turns into an ulcer (Figures 50.1 and 50.2). Most patients have one or two lesions, usually on exposed parts of the body such as the face, arms, or legs, varying in size from 0.5 to 3 cm in diameter. Usually, lesions heal spontaneously over months or years, leaving a permanent atrophic scar.

### Incidence/prevalence

The World Health Organization considers leishmaniasis to be one of the most serious parasitic diseases, with consequences for socio-economic development in many tropical and subtropical developing countries [3,4]. Until recently, the public health impact of leishmaniasis was grossly underestimated. During the past years, the endemic regions have been spreading and there has been a sharp increase in the number of recorded cases of the disease. Approximately 350 million people are at risk of contracting the disease. CL is endemic in many countries in the Mediterranean area, the Middle East, large parts of the Indian subcontinent, Africa, and Central and South America. An estimated 1.5 million new cases of CL occur annually. However, a substantial number of cases are not recorded, as notification of the disease is compulsory in only 32 of the 98 affected countries.

## Etiology and prognosis

More than 20 recognized *Leishmania* species are responsible for both forms of visceral and cutaneous leishmaniasis in 98 countries, each one having distinct epidemiological and demographic patterns [5]. The geographical distribution of the species causing CL affects countries and territories in North Africa, the Mediterranean, the Middle East, north-eastern India, and Central Asia (the Old World), the main species are *L. major*, *L. tropica*, and *L. aethiopica*, and less frequently *L. infantum* and *L. donovani*. In Central and South America, from Texas, USA, to the north of Argentina, there are two *Leishmania* subgenera: the subgenus *Leishmania* (*Leishmania*) with *L. mexicana* and *L. amazonensis* among the main pathogenic species, and subgenus *Leishmania* (*Viannia*), with four main species, *L. braziliensis*, *L. panamensis*, *L. guyanensis*, and *L. peruviana*. The different presentations of leishmaniasis vary in their prognosis and response to therapy. In general, half of the lesions caused by *L. major* or *L. mexicana* will heal within 3 months, while those caused by *L. tropica* take longer, about 10 months, and those due to *L. braziliensis* persist much longer.

### Diagnostic tests

Clinically diagnosed CL cases should be confirmed using the traditional diagnostic techniques of smear, culture, and/or histological analysis of skin biopsies [6,7]. The polymerase chain reaction test appears to be the most sensitive single diagnostic test for skin samples and aids in identifying the infecting species. Antibodies in circulation are, in general, low or undetectable. The leishmanin test (Montenegro test) detects delayed-type hypersensitivity response; it is simple to use and highly specific, but produces negative results in some affected patients and does not distinguish between previous and current infections, which is the reason why its use remains for epidemiological studies.

### Aims of treatment

Many different treatments for CL have been described [8,9]. The pentavalent antimony derivatives meglumine antimoniate (Glucantime®, Sanofi) and sodium stibogluconate (Pentostam®





Figure 50.1 Cutaneous leishmaniasis.

produced by GSK, and the generic SSG, produced by Albert David, India) remain the mainstay of treatment. Treatments are expensive and require administration over long periods of time. An effective treatment in one area for a given organism may not work in a different geographical area or for a different organism in the same area. In these cases, efficacy also depends on the patient's response. Topical treatments are appropriate for early self-limiting lesions that are not at risk of dissemination, and are attractive options offering reduced systemic toxicity and outpatient treatment. Systemic treatments are indicated when the patient has multiple or complicated lesions or is at risk of mucocutaneous leishmaniasis. The development of drug resistance is a major concern.

### Methods of search

We included all randomized controlled trials (RCTs) by searching the Cochrane Library (July 2012), Medline (1966–July 2012), and Embase (1988–July 2012). We also use the two Cochrane systematic reviews of RCTs on interventions for Old World and American CL published in 2008 and 2009, respectively [10,11]. Respecting the last edition of this book, we have found 30 new RCTs on Old World CL and 12 RCTs on American CL.

## Questions

### What is the randomized controlled trial evidence for local treatments in Old World cutaneous leishmaniasis?

#### Efficacy

##### *Intralesional meglumine antimoniate (Glucantime) or sodium stibogluconate (Pentostam)*

We found two RCTs comparing local versus systemic therapy with antimonials. An RCT [12] in Saudi Arabia (*L. major*) compared intralesional meglumine antimoniate 0.2–0.8 mL/lesion every other day over a 30-day period with 12 intramuscular injections of 15 mg/kg per day meglumine antimoniate 6 days a week. Complete cure at the end of treatment was in 68.6% (48/70) and 59.7% (46/77) of lesions, respectively. An RCT [13] from Afghanistan compared intralesional stibogluconate for up to 29 days with intramuscular stibogluconate daily for 21 days. Two months after treatment, results showed complete cure of participants in 47.3% (70/148) and 18% (26/144) of the intralesional and intramuscular stibogluconate groups, respectively.



Figure 50.2 Ulcerative cutaneous leishmaniasis.

ralesional stibogluconate for up to 29 days with intramuscular stibogluconate daily for 21 days. Two months after treatment, results showed complete cure of participants in 47.3% (70/148) and 18% (26/144) of the intralesional and intramuscular stibogluconate groups, respectively.

An RCT [14] in Pakistan (*Leishmania* spp. not reported) compared different intralesional therapeutic regimens – that is, weekly intralesional meglumine antimoniate with intralesional meglumine antimoniate fortnightly – both until complete cure or up to 8 weeks. Complete cure 2 months after therapy was observed in 92% (102 of 111) in comparison with 85.6% (89 of 104) of the lesions, respectively.

An RCT from Iran [15] (*Leishmania* not specified) compared conventional intralesional injections of 0.1 mL meglumine antimoniate with mesotherapy gun intralesional injections. There was complete cure at 3 months after treatment in 86.66% (26/85) and 83.33% (25/85) of patients, respectively.

##### *Topical paromomycin (aminosidine)*

We found three RCTs comparing topical paromomycin with placebo. A double-blind RCT [16] from Tunisia (*L. major*) compared 15% paromomycin and 10% urea with placebo twice daily for 14 days. The results at 105 days showed a complete cure in 63% (36/57) and 65.5% (38/58) of the patients, respectively. A big double-blind RCT [17] in Iran (*L. major*) compared 15% paromomycin and 10% urea with a placebo, both twice a day for 14 days. The results at 105 days showed definitive cure in 68% of patients treated with the drug compared with 68% with the placebo. Another small double-blind RCT [18] in Iran (*L. major*) compared 15% paromomycin and 10% urea with placebo twice daily for 30 days. The results at 60 days showed definitive cure in 17% compared with 20% of the patients, respectively.

We found an RCT of different regimens of paromomycin. A double-blind RCT [19] from Iran (*L. major*) compared paromomycin ointment regimens of two applications per day for 4 weeks and for 2 weeks. Complete cure at 105 days was observed in 50% (58/117) compared with 37% (43/116) of the patients, respectively.

We found two RCTs comparing paromomycin with antimonials. An unblinded RCT [20] in Iran (*L. major*) compared topical 15% paromomycin and 10% urea twice per day and intralesional 1.5 g/5 mL meglumine antimoniate weekly for a maximum of 90



days. The results at less than 2 months after treatment showed complete cure in 16.6% (eight of 48) compared with 41.7% (20 of 48), respectively. Another open RCT [21] in Iran (*L. major*) compared topical 15% paromomycin and 10% urea twice per day, with intralesional 1 mL meglumine antimoniate every other day, both for 20 days. The results at 1 week after treatment showed complete cure in 66.7% (20/30) compared with 60% (18/30), respectively.

We found an open RCT [22] from Turkey (*L. tropica*) that compared 15% paromomycin and 12% methylbenzothonium chloride twice per day for 15 days with 400 mg/day oral ketoconazole for 30 days. One month after the end of treatment, there was complete cure in 37.5% (15/40) of patients compared with no complete cure in any of the patients, respectively.

An RCT [23] from Iran (*L. major*) compared topical paromomycin-methylbenzothonium chloride applied topically twice daily for 28 days with topical photodynamic therapy every week for 4 weeks and with placebo topically twice daily also for 28 days. Two months after treatment, there was complete cure in 41.2% (14/34), 93.5% (29/31), and 13.3% (4/30) of lesions, respectively.

### Intralesional zinc sulfate solution

We found four RCTs comparing intralesional zinc sulfate with antimonials. An RCT [24] in Iran (*L. major*) compared 2% zinc sulfate solution with meglumine antimoniate, both with up to six weekly intralesional injections. Five weeks after treatment, there was complete cure in 22.6% (12/53) and 50.9% (27/53), respectively. Another RCT [25] in Iran (*L. major*) compared intralesional 2% zinc sulfate with intralesional meglumine antimoniate. At 6 weeks posttreatment, the complete cure rates were 83.87% and 60%, respectively. An RCT [26] in Iraq compared intralesional 2% zinc sulfate with intralesional 100 mg/mL sodium stibogluconate. After 6 weeks, a total of 94.8% (36/38) compared with 88.5% (31/35) of the lesions were cured, respectively. An RCT [27] from Iran compared 0.2–0.5 mL intralesional 2% zinc sulfate solution per lesion twice within 2 weeks and intralesional Glucantime weekly injected in the lesions for 6 weeks. After 8 weeks, complete cure rates were 33.3% and 80%, respectively.

### Thermotherapy

We found four RCTs comparing thermotherapy with antimonials. An RCT [13] from Afghanistan (*L. tropica*) compared thermotherapy using radiofrequency waves with intralesional stibogluconate for up to 29 days and intramuscular stibogluconate daily for 21 days. Two months after treatment, results showed that complete cure of participants accounted for 54% (75/139), 47.3% (70/148), and 18% (26/144), respectively. An RCT [28] from Iran (*Leishmania* not reported) compared localized heating using a radiofrequency heat generator and intralesional meglumine antimoniate for 4 weeks. Six months after treatment, results showed complete cure of participants in 80.7% (46/57) and 56.7% (34/60), respectively. An RCT [29] performed in Washington, DC, with patients infected in Iraq or Kuwait (*L. major*) compared one session of local 50°C heat therapy with 20 mg/kg per day of intravenous sodium stibogluconate infused over 10–50 min for a total of 10 doses. In an intent-to-treat analysis, the per-subject efficacy at 2 months was 48% and 54%, respectively, and the per-lesion efficacy was 73% and 59%, respectively. Another RCT [30] from Afghanistan (*L. tropica*) compared a single localized treatment of thermotherapy with 5 days of intralesional administration of Glucantime. At 6 months, the cure rates were 82.5% and 74%, respectively.

### Cryotherapy

We found five RCTs comparing cryotherapy with antimonials. An RCT [31] from Iran (*Leishmania* not reported) compared cryotherapy plus intralesional meglumine antimoniate versus cryotherapy and intralesional meglumine antimoniate alone, both every 2 weeks. At the end of the treatment, there was a complete cure of lesions in 80.5% (120/149), 52.2% (120/230), and 52.5% (84/160) in the respective groups. An RCT [32] from Iran (*L. tropica*) in children compared cryotherapy with liquid nitrogen applied twice to the lesion repeated weekly up to 6 weeks with intralesional Glucantime. Complete response rate at 6 months after treatment in the intention-to-treat analysis was 52.5% (21/40) and 25.6% (10/39), respectively. Another RCT [33] from Iran (*Leishmania* not reported) compared a combination of cryotherapy and intralesional meglumine antimoniate with cryotherapy alone and intralesional meglumine antimoniate monotherapy. The authors reported complete cure of participants in 89% (18/20), 67.8% (14/20), and 75% (15/20) of the respective groups, although they did not report the time of this assessment. An RCT [34] from Iran compared a combined triple therapy of cryotherapy, paromomycin cream plus intralesional meglumine antimoniate, with intralesional meglumine antimoniate monotherapy. At 6 weeks after treatment, complete cure of participants was 89.5% (68/81) and 70.4% (57/76) of the respective groups. An RCT [35] from Iran (*L. tropica*), compared CO<sub>2</sub> laser therapy with cryotherapy biweekly plus intralesional meglumine antimoniate weekly. At 12 weeks, complete cure was 93.7% (89/95 lesions) and 78% (74/95 lesions), respectively.

### Antibiotics

An RCT [36] from Iran (*Leishmania* not reported) compared weekly intralesional Glucantime injections (150–600 mg) with weekly intralesional injections of metronidazole (2.5–10 mg). In the former group, 13 patients recovered with eight injections (81%) and in the latter group only three patients recovered with eight injections (16.6%).

An RTC [37] in Iraq (*L. tropica* and *L. major*) compared intralesional injection of ciprofloxacin solution 0.2% (2 mg/mL) with intralesional 7% sodium chloride hypertonic solution. After 8 weeks, lesions assigned to ciprofloxacin showed an 81.5% healing rate with an average scar size reduction of 68.6%. Lesions assigned to sodium chloride treatment were completely healed (with or without scarring) in 76.2% of cases, and, when a scar remained, the scar size was reduced 66.0% compared with the original lesion.

An RTC [38] from Tunisia and France (*L. major*) compared a third-generation aminoglycoside ointment (WR279,396) applied twice daily for 20 days with placebo. At 80 days after treatment, in the intent-to-treat analysis, complete clinical response was observed in 94% (47/50) and 71% (30/42) of participants, respectively.

### Other

We found very limited RCT evidence for the lack of efficacy of treatments such as garlic cream [39], cream containing interferon beta [40], topical opium [41], intralesional interferon gamma [42], topical honey-soaked gauze and intralesional meglumine antimoniate in a duplicated study [43,44], topical 5% imiquimod cream plus intramuscular meglumine antimoniate [45], and topical antifungals [46,47].

We found very limited RCT evidence for the efficacy of a topical herbal extract [48], topical diminazene solution of cetrimide (Savlon) with chlorhexidine [49], intralesional 7% hypertonic

sodium chloride [25,36,50], CO<sub>2</sub> laser [34,51], and trichloroacetic acid [52].

### Drawbacks

Pain (sometimes severe pain) at the site of injection is frequently described in intralesional treatments. No other adverse reactions or local reactions were significantly reported. An appreciable number of cases of irritant contact dermatitis have been reported with topical paromomycin. Postinflammatory hypopigmentation and hyperpigmentation and burns have been described with cryotherapy and thermotherapy.

### Comment

We found 44 RCTs that covered at least 21 different local treatments for Old World CL, which could be broadly categorized into seven main groups: antimonial drugs, topical paromomycin, intralesional zinc sulfate solution, thermotherapy, cryotherapy, antibiotics, and other therapies.

Most of the trials are relatively adequate in size, with short follow-up periods. In comparisons with placebo or no treatment, some trials showed variable rates of self-healing. The results of some of the studies are difficult to interpret owing to unusually low cure rates in the group treated with antimonials.

### Implications for practice

The mainstay of local treatments for Old World CL has been the intralesional injection of antimony compounds, which have been extensively used as controls in RCTs for several newer treatments. Local treatment is appropriate for patients with early, not very inflamed, lesions on cosmetically or functionally important sites, but an expectant approach may also be appropriate in Old World endemic areas, due to rapid spontaneous healing and the development of protective immunity.

To limit toxicity, antimony derivatives have been used intralesionally for localized Old World CL. There are some RCT data on the usefulness of intralesional administration of meglumine antimoniate in comparison with other local and systemic treatments. It was difficult to evaluate the efficacy of any of the multiple current intralesional or intramuscular antimony regimens in the absence of any placebo-controlled trial. Local pain and time-consuming intralesional treatments have led investigators to seek pain-free and easier treatment modalities such as paromomycin ointment, but on the basis of the best evidence it is unlikely to be beneficial.

There is some RCT data on the lack of efficacy of intralesional zinc sulfate. There was some evidence to support the use of photodynamic therapy, thermotherapy, cryotherapy, and topical 5% imiquimod cream as antimonial adjuvant therapies. There was complete absence of RCT evidence for local excision, curettage, electrodesiccation, or other physical therapies.

## What is the randomized controlled trial evidence for systemic treatments in Old World cutaneous leishmaniasis?

### Efficacy

#### *Intramuscular/intravenous meglumine antimoniate or stibogluconate*

We found three RCT comparing different systemic antimonial therapeutic regimens. An RCT [53] performed in Pakistan (*L. tropica*) compared intramuscular meglumine antimoniate (20 mg/kg per day, maximum 850 mg) for 21 days, intralesional meglumine antimoniate (0.5 mL) into each lesion plus intramuscular meglu-

mine antimoniate (20 mg/kg per day, maximum 850 mg) for 21 days, and no treatment. Complete cure was achieved in 55% (11/20), 75% (15/20), and 10% (2/20), respectively. A double-blind RCT [54] performed in Iran (*L. major* and *L. tropica*) compared intramuscular 60 mg/kg per day Glucantime for 3 weeks, intramuscular 30 mg/kg per day Glucantime and 40 mg of the oral omeprazole for 3 weeks, and intramuscular 30 mg/kg per day Glucantime for 3 weeks. Rate of complete response at 12 weeks after treatment was 93%, 89%, and 80%, respectively. A blinded RCT [55] from Iran (*L. major*) compared oral pentoxifylline plus intramuscular meglumine antimoniate with intramuscular meglumine antimoniate for 20 days. Three months after treatment, complete cure of participants occurred in 81.3% (26/32) and 50% (16/32), respectively.

#### *Oral itraconazole*

We found six RCTs comparing oral itraconazole with placebo or no treatment. A small RCT [56] from Kuwait (*L. tropica* and *L. major*) compared 100 mg (or 3 mg/kg) itraconazole with placebo, both twice per day for 6–8 weeks. The results, 12 weeks after treatment, were excellent in 73% (11/15) and good in 20% (3/15) of the patients, in comparison with no signs of improvement in the placebo group. A big double-blind RCT [57] in Iran (*L. major*) compared 200 mg/day itraconazole for 8 weeks with placebo. Three months after treatment, results showed complete cure of participants in 67% (67/100) and 53% (53/100) of the respective groups. In a double-blind RCT [58] in Iran (*L. tropica* and *L. major*), 7 mg/kg per day itraconazole for 3 weeks was compared with placebo. One month after treatment, the lesions in 55% (36/65) of the patients showed a clinical and biological response compared with 41% (27/66), respectively. A small double-blind RCT [59] in India (*L. major* and *L. tropica*) compared oral itraconazole 100 mg twice per day for 6 weeks with placebo. Three months after treatment, results showed complete cure of participants in 70% (7/10) and 10% (1/10) of the respective groups. Finally, a small RCT [60] in India (*L. major* and *L. tropica*) compared 4 mg/kg per day itraconazole for 6 weeks with placebo. At the end of the treatment period, complete cure of participants occurred in 75% (15/20) and 0% (0/20) in the oral itraconazole and placebo groups, respectively. A small RCT [61] in India (*L. tropica*) compared 4 mg/kg per day itraconazole for 6 weeks with a few untreated patients. The results showed that 66.6% (10/15) of the patients were cured in comparison with no significant changes, respectively.

#### *Oral ketoconazole*

A small RCT [62] in Kuwait (*Leishmania* not reported) using oral 600 mg/day ketoconazole for 28 days was compared with oral 800 mg/day ketoconazole for 28 days. The authors did report complete cure of 66.7% (12/18) and 60% (9/15) participants in the respective groups at the end of the treatment period.

We found two RCTs comparing oral ketoconazole with antimonials. An RCT [63] in Iran (*L. tropica* and *L. major*) compared ketoconazole 600 mg/day for 30 days with intralesional meglumine antimoniate, six to eight injections biweekly. Six weeks after treatment there was a complete cure of 89% (57/64) and 72% (23/32) of participants in the respective groups. An RCT [64] in Yemen (*Leishmania* not reported) compared intralesional stibogluconate (100 mg/mL) alone, a combination of intralesional stibogluconate plus intramuscular stibogluconate, and a combination of intralesional stibogluconate plus oral ketoconazole (200 mg three times daily) for 4 weeks. Complete cure occurred in 58.3%, 93.3%, and 92.3% of lesions, respectively.

We found an open RCT [21] from Turkey (*L. tropica*) comparing 15% paromomycin and 12% methylbenzothonium chloride twice per day for 15 days with oral ketoconazole 400 mg/day for 30 days. At 4 weeks of treatment, any patient showed complete cure in the group of oral ketoconazole compared with 37.5% of patients (15 of 40) in the other group.

### Oral fluconazole

In a double-blind RCT [65] in Saudi Arabia (*L. major*), oral fluconazole 200 mg/day for 6 weeks was compared with placebo. At 3 months after treatment, complete cure of participants occurred in 63/106 (59%) and 22/103 (21%), respectively.

An RCT [66] in Iran (*L. major*) compared oral fluconazole 400 mg daily with oral fluconazole 200 mg daily. At 6 weeks, complete healing in the 400 mg group was significantly higher than in the 200 mg group (81% vs 48.3%).

### Oral dapsone

We found three RCTs comparing oral dapsone with placebo or no treatment. A double-blind RCT [67] in India (*L. major* and *L. tropica*) compared 100 mg dapsone every 12 h for 6 weeks with placebo. At 1 month after therapy, complete cure was seen in 82% (49/60) and 5% (3/60) of patients, respectively. A small RCT [59] in India (*L. major* and *L. tropica*) compared dapsone 4 mg/kg per day, itraconazole, and placebo, all for 6 weeks. Three months after therapy, complete healing was assessed in 90% (18/20), 75% (15/20), and 10% (2/20) of the patients, respectively. An RCT [68] from India (*L. tropica*) compared dapsone 2 mg/kg per day for 21 days with untreated patients. Six months after therapy, results showed cure in 80% (40/50) of the patients and failure in 10% (5/50), compared with no significant changes, respectively.

### Oral allopurinol

We found three RCTs comparing oral allopurinol with systemic antimonials. An RCT [69] in Iran (*L. tropica*) compared oral allopurinol 15 mg/kg per day for 3 weeks, intramuscular meglumine antimoniate 30 mg/kg per day for 2 weeks, and allopurinol plus meglumine antimoniate. At the end of the treatment period, complete cure of participants was in 18% (9/50), 24% (12/50), and 46% (23/50) of the respective groups. An open RCT [70] from Iran (*L. major*) compared allopurinol 20 mg/kg per day plus meglumine antimoniate 30 mg/kg per day with intramuscular meglumine antimoniate 60 mg/kg per day, both for 20 days. At 51 days after treatment there was a complete cure of participants in 69% (25/36) and 72% (26/36) of the respective groups. An RCT [71] in Pakistan (*Leishmania* not reported) compared oral allopurinol 20 mg/kg per day in three or four doses with intravenous stibogluconate 20 mg/kg per day, both for 15 days. At the end of the treatment period there was a complete cure of participants in 85% (17/20) and 70% (14/20) of the respective groups.

### Oral miltefosine

An RCT [72] from Iran (*L. major*) compared oral miltefosine for 28 days with intramuscular meglumine antimoniate for 14 days. Three months after treatment the results showed complete cure in 81.3% (26/32) and 80.6% (25/31) of participants, respectively.

### Oral antibiotics

An RCT [73] performed in Iran (*L. tropica*) compared 500 mg/day oral azithromycin for 5 days/month; treatment cycles were repeated

monthly to a maximum of 4 months with 60 mg/kg intramuscular meglumine antimoniate for 20 days. At 16 weeks, the response rates in the azithromycin group of 20 patients (29 lesions) were as follows: full improvement, 10.3%; partial improvement, 27.6%; and 62.1%, no response. In the intramuscular meglumine antimoniate group with 27 patients (58 lesions), these rates were 34.4%, 13.8%, and 51.7%, respectively.

We found three RCTs comparing oral rifampicin with placebo. An RCT [74] from Saudi Arabia (*Leishmania* not reported) compared oral rifampicin for 4–6 weeks with placebo. Three months after treatment the results showed complete cure occurred in 45.7% (21/46) and 18.8% (3/16), respectively. An RCT [75] from India (*L. tropica*) compared oral rifampicin for 4 weeks with placebo. At the end of the treatment there was complete cure in 68% (17/25) and 4% (1/25) of the participants, respectively. Another trial [76] from India (*L. tropica*) which compared oral rifampicin plus omeprazole for 6 weeks with placebo reported at the end of the treatment a complete cure of 64% (16/25) and 12% (3/25) of participants, respectively.

### Other

We found very limited RCT evidence for the benefit of oral zinc sulfate [77,78] and 100 mg artesunate plus 250 mg/12.5 mg sulfamethoxypyrazine/pyrimethamine [79].

### Drawbacks

Parenteral antimonials can produce nausea, vomiting, anorexia, diarrhea, myalgia, body aches, and liver abnormalities. The most common side effects with oral antifungals were gastrointestinal complaints and headache, but the same symptoms were reported in patients from the placebo group and none of the laboratory values were outside normal limits. With oral dapsone, side effects include nausea and anemia. With oral allopurinol, side effects include nausea, macular rash, heartburn, and a mild increase in liver enzymes. With oral miltefosine the side-effects include nausea, vomiting, abdominal pain, headache, itch, and fever.

### Comment

We found 29 RCTs that covered at least 11 different systemic treatments for Old World CL, which could be broadly categorized into nine main groups: antimonial drugs, oral itraconazole, oral ketoconazole, oral fluconazole, oral dapsone, oral allopurinol, oral miltefosine, oral antibiotics, and other therapies.

We have some concerns regarding the precision of data reported in several studies, and again unusually low cure rates in the group treated with antimonials, as well as variable rates of self-healing.

### Implications for practice

Systemic therapy in Old World CL is appropriate for patients with multiple or more complicated lesions. In these cases, pentavalent antimony compounds have been regarded as the first-line therapy. Their efficacy has been established in RCTs in comparison with other treatments, but not in comparisons between different antimonials or in comparison with a placebo.

When well tolerated and oral agents are needed or preferred, there is limited–moderate RCT evidence to support the use of oral itraconazole or fluconazole, 200 mg/day for 6–8 weeks and oral pentoxifylline as adjuvant therapy to intramuscular meglumine antimoniate. There was insufficient evidence to support the use of oral therapy with dapsone or allopurinol, miltefosine, or rifampicine.



## What is the randomized controlled trial evidence for systemic treatments in American cutaneous leishmaniasis?

### Efficacy

#### *Intravenous/intramuscular meglumine antimoniate*

We found two RCTs comparing different doses of meglumine antimoniate. An RCT [80] from Colombia (*L. panamensis*) compared 20 mg/kg per day intramuscular meglumine antimoniate once a day for 10 days with 20 mg/kg per day intramuscular meglumine antimoniate for 20 days. At 52 weeks after treatment the results showed responses in 41% (28/68) and 35% (24/68) of patients, respectively. In a small double-blind RCT [81] from Brazil (*L. braziliensis*), a high dose of intravenous meglumine antimoniate (20 mg/kg per day) was compared with a low dose of intravenous meglumine antimoniate (5 mg/kg per day), both for 30 days. At the end of treatment the results showed complete responses in 81.8% (9/11) and 83.3% (10/12) of the patients, respectively.

We found two RCTs comparing intramuscular meglumine antimoniate with intramuscular stibogluconate. In an RCT [82] in Panama (*L. braziliensis panamensis*), 20 mg/kg per day intramuscular meglumine antimoniate was compared with 20 mg/kg per day intramuscular stibogluconate, both for 20 days. At the end of treatment the results showed complete cure in 72% (21/29) and 46% (14/30) of the patients, respectively. A double-blind RCT [83] in Bolivia and Colombia (*L. braziliensis*) compared 20 mg/kg per day intramuscular meglumine antimoniate; 20 mg/kg per day intramuscular stibogluconate (Pentostam), and stibogluconate (generic), all for 20 days. At 6 months the results showed complete cure in 76% (38/50), 75% (12/16), and 83% (40/48) of patients, respectively.

#### *Intravenous/intramuscular stibogluconate*

We found two RCTs comparing different doses of stibogluconate. A small double-blind RCT [84] in Panama and Central America (*L. braziliensis panamensis*) compared 10 mg/kg per day stibogluconate, with 20 mg/kg per day stibogluconate, both for 20 days. Complete cure occurred in 76% (16/21) and 100% (19/19) of participants in the respective groups 1.5 months after treatment. A small RCT [85] of US military personnel compared 600 mg intravenous stibogluconate once daily for 10 days by rapid infusion, 600 mg/day intravenous stibogluconate followed by a continuous infusion of 600 mg stibogluconate for 24 h every day for 9 days, and stibogluconate loading dose of 600 mg followed by 200 mg stibogluconate every 8 h for 9 days. Complete cure occurred in 100% (12/12), 50% (6/12), and 42% (5/12) of participants in the respective groups at the end of treatment. A small RCT [86] of US military personnel was excluded because of mixed Old World and American forms of CL.

#### *Intravenous/intramuscular paromomycin*

We found two RCTs comparing paromomycin with antimonials. A small open RCT [87] in Brazil (*L. braziliensis*) compared 4 mg/kg per day intramuscular pentamidine on alternative days up to a total of eight injections, 20 mg/kg per day intramuscular paromomycin for 20 days, and 10 mg/kg per day intramuscular meglumine for 20 days. At 3 years after the end of treatment, all of the patients in the paromomycin and pentamidine groups were cured. An open RCT [88] in Belize (*L. braziliensis* and *L. mexicana*) compared intravenous paromomycin 14 mg/kg per day with intravenous sodium stibogluconate 20 mg/kg per day, both for 20 days. Complete cure occurred in 59% (10/17) and 88% (15/17) of participants in the respective groups 1.5 months after treatment.

An RCT [89] from Colombia (*L. panamensis*) compared parenteral 12 mg/kg per day paromomycin for 7 days, parenteral 12 mg/kg per day paromomycin for 14 days, and parenteral paromomycin 18 mg/kg per day for 14 days. At 12 months after treatment the results showed cures in 10% (3/30), 45% (13/29), and 50% (15/30) of patients, respectively.

#### *Oral ketoconazole*

An RCT [90] in Guatemala compared 600 mg/day oral ketoconazole for 28 days, 20 mg/kg per day intravenous stibogluconate for 20 days, and placebo. Complete cure occurred in 52% (12/23), 96% (24/25), and 20% (3/15) of participants in their respective groups 2 months after treatment. Another RCT [91] from Panama (*L. braziliensis*, *L. panamensis*) compared oral 600 mg/day ketoconazole for 28 days, 20 mg/kg intramuscular stibogluconate for 20 days, and placebo. At 3 months the results showed cures in 73% (16 of 22), 68% (13 of 19), and none of the patients, respectively.

#### *Oral allopurinol*

We found three RCTs comparing oral allopurinol with meglumine antimoniate. An open RCT [92] in Colombia (*L. braziliensis panamensis*) compared 20 mg/kg per day intramuscular meglumine antimoniate for 15 days, oral allopurinol plus 20 mg/kg per day intramuscular meglumine antimoniate in four divided doses for 15 days, 20 mg/kg per day oral allopurinol in four divided doses for 15 days, and untreated patients. At 12 months after treatment the results showed cures in 36% (12 of 33), 74% (26 of 35), 80% (20 of 23), and 0%, respectively. An open RCT [93] in El Salvador (*L. braziliensis braziliensis*) compared 10 mg/kg per day intravenous meglumine antimoniate once a day with 20 mg/kg oral allopurinol three times a day, both for 20 days. At 3 months the results showed healed lesions in 50% (8/16) of the patients and no healed lesions (one progressed to mucosal disease), respectively. A double-blind RCT [94] in Colombia (*L. panamensis*) compared 20 mg/kg per day intramuscular meglumine antimoniate for 20 days, three tablets of allopurinol 100 mg four times daily (20 mg/kg per day) for 28 days, and placebo. At 12 months the results showed cures in 92% (52 of 56), 32.7% (18 of 55), and 37% (17 of 46) of the patients, respectively.

We found two RCTs comparing oral allopurinol with stibogluconate. An open RCT [95] in Colombia (*L. braziliensis panamensis*) compared 20 mg/kg per day stibogluconate for 15 days with 20 mg/kg per day stibogluconate for 15 days plus oral allopurinol 20 mg/kg per day also for 15 days. At 12 months after therapy, 39% of the patients (19/49) were cured, 14% (7/49) relapsed, and the treatment failed in 43% (21/49), compared with cures in 71% (36/51), relapses in 27% (14/51), and treatment failure in 12% (6/51), respectively. An RCT [96] in Ecuador (*L. panamensis*) compared 20 mg/kg per day intramuscular stibogluconate for 20 days, oral allopurinol ribonucleoside (1500 mg q.i.d.) plus oral probenecid for 28 days, and no treatment. At 12 months the results in the stibogluconate group showed cures in 96.4% (27/28) of the patients. In the allopurinol group, 42.8% (9/21) of the patients were cured, and the treatment failed in 10 patients. In the untreated group, 75% (9/12) of the patients were cured and the treatment failed in three patients.

#### *Intramuscular pentamidine*

We found two RCTs comparing intramuscular pentamidine with antimonials. An open RCT [86] in Brazil (*L. braziliensis*) compared 10 mg/kg per day intramuscular meglumine for 20 days with 4 mg/kg per day intramuscular pentamidine, on alternative days, up to a



total of eight injections. At 3 years, only one patient in the meglumine group did not achieve a cure, and all of the other patients were cured. An open RCT [97] in Peru (*L. braziliensis*) compared 20 mg/kg per day intravenous meglumine antimoniate for 20 days with 2 mg/kg intramuscular pentamidine every other day, up to a total of seven injections. At 6 months, cures were observed in 78% (31 of 40) and 35% (14 of 40) of the patients, respectively.

### Oral miltefosine

An RCT [98] from Colombia and Guatemala (*L. braziliensis*, *L. panamensis*, and *L. mexicana*) compared oral miltefosine for 28 days with placebo. Six months after treatment the oral miltefosine had significantly higher cure rates than placebo in the Colombian site but not in the Guatemala site.

We found five RCTs comparing oral miltefosine with antimonials. An RCT [99] from Brazil (*L. braziliensis*) compared miltefosine with pentavalent antimony. Six months after treatment, in the intention-to-treat analyses, the definitive cure rate was 75% and 53.3%, respectively. Miltefosine was more effective than the antimonial in the 13–65-years-old age group compared with the 2–12-years-old group. An RCT [100] from Bolivia (*L. braziliensis*) compared oral miltefosine (2.5 mg/kg per day) for 28 days with intramuscular antimony (20 mg/kg per day) for 20 days. The cure rates with 6 months of follow-up were statistically similar: 36 of 41 evaluable miltefosine patients (88%) versus 15 of 16 (94%) evaluable antimony patients. However, antimony cured more rapidly. An RCT [101] from Brazil (*L. (Viannia) guyanensis*) compared oral miltefosine (2.5 mg/kg per day/28 days) in 60 patients with parenteral antimony (15–20 mg/kg per day/20 days) in 30 patients according to age groups: 2–12 years old and 13–65 years old. Cure rates at 6 months were 71.4% and 53.6% for miltefosine and the antimonial, respectively. There were no differences in cure rates between age groups within the same treatment arms. An RCT [102] conducted in Colombian army population (*L. (Viannia) braziliensis* or *L. (Viannia) panamensis*) compared 50 mg oral miltefosine three times per day for 28 days with 20 mg/kg of meglumine antimoniate per day for 20 days by intramuscular injection. The efficacy of miltefosine by protocol was 69.8% (85/122 patients) and 58.6% (85/145 patients) by intention to treat. For meglumine antimoniate, the efficacy by protocol was 85.1% (103/121 patients) and 72% (103/143 patients) by intention to treat. A single-blinded RCT [103] conducted in children from Colombia (*L. panamensis* and *L. guyanensis*) compared 20 mg/kg per day of intramuscular meglumine antimoniate for 20 days with oral miltefosine (1.8–2.5 mg/kg per day for 28 days). By intention-to-treat analysis, failure rate was 17.2% for miltefosine and 31% for meglumine antimoniate.

### Other treatments

We found very limited RCT evidence for the efficacy of other systemic treatments, such as immunotherapy with a parasite-derived antigen [104], associated vaccines [105], oral azytromycin [106], and adjuvant interferon gamma in intravenous meglumine antimoniate therapy [107].

We also found limited RCT evidence of lack of efficacy of oral mefloquine [108], early treatment versus deferred treatment of intestinal helminth infection on the clinical course of patients with CL treated with pentavalent antimony [109], and imiquimod in combination with pentavalent antimony [110].

### Drawbacks

The more frequent side effects of meglumine antimoniate are arthralgias, myalgias, asthenia, malaise, nausea, pruritus, headache,

and fever. There was no evidence of liver, cardiac, bone marrow, or kidney toxicity. The symptoms reported with stibogluconate include cases of pancreatitis, but no other significant side effects. Intramuscular paromomycin produced myalgias, anorexia, and asthenia. Even in some trials, oral miltefosine showed no side effects different from those of the placebo; adverse gastrointestinal events (vomiting, nausea, abdominal pain, and diarrhea) are generally associated with the use of miltefosine.

The only severe side effects attributable to allopurinol were headache and epigastric pain. Pentamidine produced cases of hypotension, hypoglycemia, headache, myalgias, anorexia, asthenia, and arthralgia.

### Comment

We found 32 RCTs that covered at least 11 different systemic treatments for American CL, which could be broadly categorized into eight main groups: intravenous/intramuscular meglumine antimoniate, intravenous/intramuscular stibogluconate, intravenous/intramuscular paromomycin, oral ketoconazole, oral allopurinol, intramuscular pentamidine, oral miltefosine, and other treatments.

The mainstay of systemic treatment for American CL is the use of pentavalent antimony compounds, which have been extensively used in practice and as controls in RCTs for newer treatments. In contrast to Old World CL, we found several RCTs comparing different antimonials. The results of some studies are difficult to interpret, as large numbers of patients were lost to follow-up.

### Implications for practice

Systemic therapy with intravenous or intramuscular pentavalent antimony compounds in American CL is regarded as being the first-line therapy, due to the progression to mucocutaneous disease in infections with *L. braziliensis*. There is moderate RCT evidence for the efficacy of these treatments.

There is moderate evidence for the efficacy of oral miltefosine. There is some RCT evidence for a lack of significant effects with oral ketoconazole (we found no RCTs for other antifungals), intramuscular pentamidine, and oral allopurinol.

### What is the randomized controlled trial evidence for local treatments in American cutaneous leishmaniasis?

#### Efficacy

##### Topical paromomycin/methylbenzothonium chloride

A double-blind RCT [111] in Guatemala (*L. braziliensis*) compared 15% paromomycin and 12% methylbenzothonium chloride twice a day for 20 days with placebo. A clinical response was observed after 12 months in 85.7% (31 of 35) and 39.4% (13 of 33) of patients, respectively. Another double-blind RCT [112] in Honduras (*L. mexicana* and *L. chagasi*) compared 15% paromomycin and 10% urea for 4 weeks with placebo. Complete cure occurred in 4.3% (1/23) and 3.3% (1/30) of participants in the respective groups 2.5 months (11 weeks) after treatment.

We found two RCTs comparing topical paromomycin/methylbenzothonium chloride with antimonials. A double-blind RCT [113] in Colombia (*L. braziliensis panamensis*) compared topical paromomycin/methylbenzothonium chloride twice a day for 10 days plus stibogluconate for 7 days, stibogluconate for 7 days, topical paromomycin/methylbenzothonium chloride twice a day for 10 days plus stibogluconate for 3 days, and injectable stibogluconate for 20 days. At 12 months the percentages of cure were 58%,

53%, 20%, and 84%, respectively. A double-blind RCT [114] in Ecuador (*L. viannia*) compared topical 15% paromomycin/12% methylbenzothonium chloride twice daily for 30 days, topical 15% paromomycin plus 10% urea twice daily for 30 days, and 20 mg/kg per day intramuscular meglumine antimoniate for 10 days. At 12 weeks after the start of treatment the percentages of cure were 57.5% (23 of 40), 52.5% (21 of 40), and 82.5% (33 of 40), respectively.

### Thermotherapy

We found two RCTs comparing thermotherapy with antimonials. An RCT [115] from Brazil (*L. (Viannia) braziliensis*) compared heat therapy given in a single session combined with intravascular meglumine antimoniate after day 28, with intravascular meglumine antimoniate, both for 20 consecutive days. Complete cure occurred in 5.9% (1/17) and 10% (2/20) of participants in the respective groups at the end of treatment. An RCT [116] from Guatemala (*L. braziliensis*, *L. mexicana*) applied three treatments of localized heat from a radiofrequency generator at 50°C for 30 s, at 7-day intervals compared with intramuscular meglumine antimoniate for 15 days. Complete cure 2 months after treatment occurred in 59% (13/22) and 73% (16/22) of participants in the respective groups.

### Topical imiquimod

We found two RCTs [117,118] from Peru (*L. braziliensis*, *L. peruviana*, *L. mexicana*, *L. amazonensis*) on adjuvant therapy with 5% imiquimod cream every other day for 20 days plus intramuscular meglumine antimoniate for 20 days and 7.5% imiquimod cream every other day for 20 days plus intravascular meglumine antimoniate for 20 days. There was no significant synergistic effect of topical 7.5% imiquimod combined with intravascular meglumine antimoniate in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, or *L. peruviana* infections and no synergistic effect of topical 5% imiquimod combined with intramuscular meglumine antimoniate in *L. peruviana* and *L. braziliensis* infections. Topical 7.5% imiquimod had significantly lower cure rates than intravascular meglumine antimoniate in *L. braziliensis*, *L. amazonensis*, *L. mexicana*, and *L. peruviana*.

### Other treatments

We found limited RCT evidence for the efficacy of other treatments, such as WR279,396 (composed cream) [119] or adjuvant topical human granulocyte-macrophage colony-stimulating factor [120,121]. We also found limited RCT evidence of lack of efficacy of topical nitric oxide-releasing patches [122].

### Drawbacks

Side effects reported in topical paromomycin therapy included local pruritus, a burning sensation, local pain, and local edema. No significant adverse effect was seen or reported by heat therapy.

### Comment

We found 12 RCTs that covered at least six different local treatments for American CL, which could be broadly categorized into four main groups: topical paromomycin/methylbenzothonium chloride, thermotherapy, topical imiquimod, and other treatments.

### Implications for practice

Local therapy in American CL is an option only for patients who are not at risk of mucocutaneous disease and with early, not very inflamed lesions. However, there is no good RCT evidence to recommend any of the local treatments described. There is some RCT

evidence for the lack of efficacy of paromomycin or synergistic topical imiquimod. There was insufficient RCT evidence to make recommendations on thermotherapy.

### Key points

- In our search for the best available evidence on treatments for CL, we found 44 RCTs (21 different treatments) of local therapies and 29 RCTs (11 different treatments) of systemic therapies for Old World CL. For American CL, there were 32 RCTs (11 different treatments) of systemic therapies and 12 RCTs (six different treatments) of local therapies.
- There is a definite need to identify less-expensive, painless, and safer treatments for CL, but definitive recommendations are limited as there have been few rigorously designed randomized clinical trials.
- Varying susceptibility to the different species of *Leishmania* that occur in different geographical regions needs to be taken into account in the response to treatment.
- The development of drug resistance is a major concern when evaluating old trials.
- There is a need that lessons learned from previous research can better influence future clinical research in CL [123].

### Therapies for Old World cutaneous leishmaniasis

- An expectant approach may be appropriate in Old World endemic areas, in view of rapid spontaneous healing and the development of protective immunity in most cases.
- Pentavalent antimony compounds are considered to be the first-line therapy. Local treatment is used for patients with early, not highly inflamed, lesions on cosmetically or functionally important sites. Systemic therapy may be appropriate for patients with multiple or more complicated lesions.
- The range of affordable and painless treatment modalities includes oral drugs, but on the basis of the best present evidence the latter are unlikely to be beneficial. If well-tolerated oral agents are needed or preferred, then there is limited RCT evidence to support the use of oral itraconazole or fluconazole.

### Therapies for American cutaneous leishmaniasis

- Although systemic therapy with pentavalent antimony compounds may be expensive and their administration is associated with severe adverse effects, they are still the first-line drugs for American CL. Oral miltefosine can be used depending on the species causing the infection.

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**Background****Definition**

Scabies is an itchy immune hypersensitivity reaction to infestation of the skin by the mite *Sarcoptes scabiei*. Fertilized adult female mites burrow through the skin at the junction of the stratum corneum and the prickle cell layer, where they lay their eggs. Burrows are pushed out progressively towards the skin surface with the stratum corneum. Adult males and juvenile mites (larvae and nymphs) live mostly on the skin surface, but may make temporary burrows for molting from one development stage to another.

Infestation of immune-competent people is most common on the hands, digits and finger webs, and on the wrists. The flexor surfaces of the elbows, the axillae, ankles, buttocks, breasts, and male genitalia may also be infested. In the elderly, infants, and the immunocompromised, the infestation may be more diffuse, including the head and neck, and palms and soles.

**Incidence/prevalence**

We found no recent published data on the incidence or prevalence from any developed country. Scabies is a common public health problem in developing countries, where the prevalence may exceed 50% in some communities, and the prevalence has been estimated at 300 million cases worldwide [1]. Older studies have shown that the prevalence is highest in teenagers and schoolchildren [2–4]. However, the incidence has increased recently in the institutionalized elderly in nearly all countries. Historical data from Denmark show that epidemic cycles arise at 15–20-year intervals [2].

**Etiology/risk factors**

Transmission of scabies mites occurs during relatively prolonged skin–skin contact. The infection is most frequent in communities with long-term conditions of overcrowding, and is believed to increase following social disruption. Reduction of immune competence increases the risk of contracting infestation, with a concomitant risk of high mite numbers. We found no evidence that hygiene influences the risk, although good hygiene may ameliorate symptomatic presentation [5].

**Prognosis**

Scabies is not life threatening, but the severe, persistent itch and secondary infections may be debilitating and disfiguring. Long-term infestations are inherently immunodepressive and in susceptible people may lead to the development of a form of the disease in which large numbers of mites inhabit hyperkeratotic plaques. These shed skin plaques may be a source of reinfection and transmission [6]. In some circumstances, scabies infected with hemolytic streptococci may result in acute glomerulonephritis [5].

**Diagnosis**

A diagnosis of active infestation is confirmed only by finding mites, mite ova, or fecal pellets (scybala) (parasitological diagnosis). Dermoscopy and videodermoscopy may be more reliable methods for finding mites than skin scraping or other similar methods [7,8]. Mite burrows in the skin, the distribution of papular lesions, and bilateral itch not affecting the head, chest, or back are indicative (clinical diagnosis), as is clustering of cases of nocturnal pruritus associated with a rash in household contacts; but these findings are not confirmation of an active infestation. Nodular lesions around the axillae, navel, or on the penis or scrotum are pathognomonic, but may persist for months after cure.

**Aims of treatment**

The aim of treatment is to eliminate infestation by killing all mites and their eggs.

**Outcomes**

There are no established standard criteria for making a diagnosis or judging treatment success. Trials have used different methods, and in many cases the method was not stated. Treatment success should be given as the percentage of people completely cleared of scabies mites, ova, or fecal pellets in skin scrapings viewed under magnification. Clinical success includes elimination of papular and vesicular eruptions and pruritus. Ideally, outcomes should be assessed 28 days after the start of treatment, but interim assessments contribute to the clinical and parasitological picture. This allows time for lesions to heal, but assessment after 28 days risks

confounding of the result through reinfestation. If treatment fails, eggs hatch within 3 days, and emerging mites become mature 9–10 days later.

### Methods of search

- The initial search conducted for a systematic review compiled in 2010 [9] used the following primary sources: Cochrane Infectious Diseases Group Specialized Register; Medline, Embase, LLACS, IndMED, and grey literature.
- Medline update search for evidence-based dermatology, May 2012.
- Google Scholar search, June 2012.
- Manual searching of relevant journals.

### Context

Overall, studies in this therapeutic area are mostly either poorly designed or else poorly reported; in some cases it is difficult to determine just what the investigators did with their patients. Consequently, evaluation is often difficult and, because the studies are frequently too small to draw adequate conclusions unless there is a wide disparity in outcome between interventions, difficult to determine their practical value. Using the standard approach to clinical trial statistics, nearly all studies are too small to conclude equivalence, even with extremely wide, and therefore unacceptable, margins. Consequently, the only method of conventional analysis is to test for either noninferiority or more rarely superiority, and in most cases the studies are too small and too heterogeneous to conclude either. However, in many cases the authors' analyses are only given on the per-protocol (PP) compliant group of participants rather than the standard norm for clinical evaluation of the intention-to-treat (ITT) group. As a result, the reported outcome data are often optimistic given that several studies experienced a high level of drop-out or participants lost to follow-up.

A further significant drawback is that several studies attempted to compare too many therapeutic options concurrently. Nevertheless, many authors attempt to draw conclusions with a level of confidence not justified by the data. Such weaknesses are also compounded by poor reporting of factors such as use of retreatments, and in respect of the outcome criteria there are few consistencies

of approach to confirmation of initial infestation or adequate freedom from mites after treatment.

Although symptoms of scabies infestation may be relatively clear, especially in communities where the infestation may not be “modified” in presentation by earlier inadequate treatments, there is a need to demonstrate mites prior to initiating study treatment. This is especially important because most studies are conducted in resource-poor countries where the presentation of the disease may often be modified by secondary infection.

Since the last edition, no new or original developments have occurred in scabies treatment, and with resistance to all treatments a potential problem the dosing and application regimen may actually be more important than the material used.

### Questions

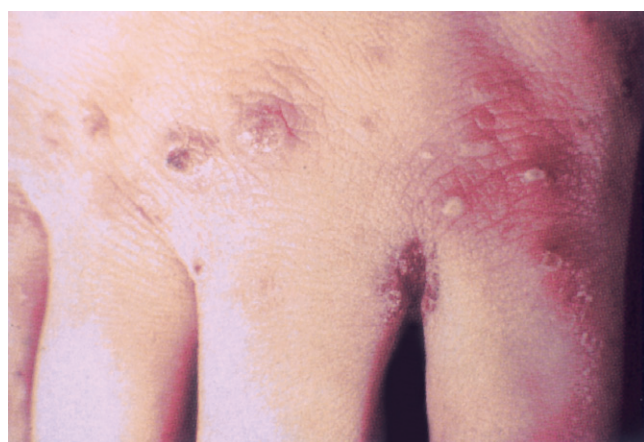
**How successful are topical treatments for scabies? For example, would a topical treatment be suitable for treating newly diagnosed scabies in a 16-year-old girl?**

**Insecticide-based pharmaceutical products**

#### Benefits

We found one systematic review (search date 2010) that examined 22 trials (18 compared drug treatments, one was placebo controlled, three compared treatment regimens, and one compared the drug vehicles). In each case, a single application of treatment was given, unless stated otherwise.

One study (150 adults and children) compared 5% permethrin cream with 10% crotamiton cream (a noninsecticide) and 1% lindane lotion [10]. It used clinical features as the measure of success (Figure 51.1). The results showed that, at 28 days, permethrin was slightly, but not significantly, more likely to cure patients receiving it (49 of 50; 98%), versus 44 of 50 (88%) with crotamiton. The same study also found that permethrin was significantly more effective than lindane, which cured only 12 of 50 (24%) people (relative risk, 4.08; 95% confidence interval [CI], 2.5–6.7) [10]. A single randomized controlled trial (RCT) comparing 5% permethrin cream with 10% crotamiton cream evaluated cure by elimination of parasites [11]. It found that permethrin was more effective after 14 and



(a)



(b)

**Figure 51.1** (a) Papules, pustules, and impetiginization in the vicinity of scabies burrows and (b) excoriated rash and papules on the wrists in simple scabies.

28 days. After 14 days, 33 of 47 people in the permethrin group (70%) and 41 of 47 in the crotamiton group (87%) still had lesions. At this point, 10 people in the crotamiton group were withdrawn from the study because their infestation was exacerbated. However, after 28 days, 42 of 47 people in the permethrin group (89%) were free from parasites, in comparison with 28 of 47 (60%) in the crotamiton group [11]. This study also recorded patients' subjective reports on the persistence of pruritus, which was found to be closely related to the effectiveness of the treatments.

Three trials compared the effect of 5% permethrin cream with that of 1% lindane lotion. A small study (including 46 patients) found that fewer people improved 14 days after using permethrin (13 of 23; 57%) in comparison with lindane (20 of 23; 87%;  $P < 0.02$ ), but there was a significantly better rate of cure, by parasitological examination, for permethrin at 28 days (21 of 23 vs 15 of 23;  $P < 0.025$ ) [12]. A larger trial (including 467 patients) did not identify parasites, but recorded a significant decrease in the number of lesions persisting in both groups after  $14 \pm 3$  days. At  $28 \pm 7$  days there was no significant difference in the success rates, with 181 of 199 (91%) cured using 5% permethrin cream, compared with 176 of 205 (86%) using 1% lindane lotion [13]. At the final assessment, significantly fewer of the patients in the permethrin group (27 of 194; 14%) had a persistent itch, in comparison with 49 of 197 (25%) in the lindane group ( $P = 0.007$ ) [13].

A medium-sized randomized, double-blind, crossover study (117 patients aged 6–64 years, plus contacts), conducted in Iran, investigated treatment with either 1% lindane cream or 5% permethrin cream [14]. Both treatments were applied for 12 h and repeated after 7 days. However, there were 11 drop-outs from the lindane group and seven from the permethrin group, not adequately explained by the authors. At 2 weeks, 44 of 52 (84.6%) had improved with permethrin and 23 of 47 (48.9%) with lindane. After 14 days, those considered still to be infected, using a mixture of parasitological and clinical criteria, were switched to the other treatment regimen. After 4 weeks, one person originally treated with permethrin and then retreated with lindane still showed severe pruritus. There were two irritation adverse events in the permethrin group and one in the lindane group.

We also found one previously unreviewed hospital-based RCT (80 patients aged 3–60 years), conducted in Pakistan, comparing 1% lindane cream with 5% permethrin cream [15]. No details of randomization method were given, and parasitological confirmation of infestation was made in 43 of the 80 (53.8%) participants. Products were administered at home, but no information on blinding was given. Follow-ups were made at 7, 14, and 28 days. Two patients lost to follow-up were not counted in the analyses by the authors. Confusingly, actual outcome data were not given, but it can easily be worked out that cure (not defined) for the ITT group was achieved for 35 of 40 people (87.5%) in the lindane group and also for 35 of 40 (87.5%) in the permethrin group. There were more adverse events, such as burning paresthesia and pruritus in those treated with permethrin, 10 of 40 people (25%) compared with six of 38 (16%) treated with lindane.

An observational multicenter study conducted in Germany (106 children and adults, aged 3 months–71 years) received a single application of 5% permethrin cream and were assessed after 14 and 28 days [16]. People who were not considered cured by dermatoscopy on day 14 were retreated, and 95.1% of the participants were diagnosed as being free from infection on day 28.

Two RCTs conducted in Italy evaluated synergized pyrethrins foam (0.16% pyrethrins, 1.65% piperonyl butoxide). In one study

(40 adults, 18–75 years) it was compared with 5% permethrin cream [17]. Both treatments were applied three times for 8 h on days 0, 1, and 14. Efficacy was assessed blindly on day 14 using a mixture of clinical criteria, but an itch index was used as the main criterion of success. A second assessment was made after 4 weeks. The foam was found to produce a significant difference ( $P = 0.013$ ) in reducing the number of lesions and the itch index at day 14 in comparison with permethrin, and the difference increased to  $P = 0.0001$  by the 4-week evaluation. The second RCT (including 240 convicted prisoners) compared three applications of synergized pyrethrins foam on consecutive days with five consecutive applications of benzyl benzoate lotion [18]. After 2 weeks, 90 of 120 of the patients in the group treated with pyrethrins (75%) were judged clinically cured, in comparison with 85 of 120 (71%) in the benzyl benzoate group. Those not considered cured were given another course of treatment with the same material, and after 4 weeks the cure rates were 95% and 91%, respectively. Those not considered cured still complained of itching. Burning and irritation due to treatment was significantly ( $P = 0.0001$ ) more common in the benzyl benzoate group, in which only 41% of participants showed good tolerability, compared with 95% in the pyrethrins group.

The systematic review identified no RCTs comparing 0.5% malathion. Anecdote suggests it is of diminishing effectiveness, and malathion products are no longer available in several countries where formerly used.

### Drawbacks

Only minor adverse effects have been reported for most insecticides. The exception is lindane, for which there are extensive reports of effects related to overdosing and absorption [19–21]. Because of recognized neurotoxicity, lindane is now restricted to second-tier use or is banned in most developed countries. However, it is still used in some resource-poor countries partly because alternatives are not readily available or are too expensive. Lindane passes transdermally during treatment and other exposures, and may be stored in fatty tissues and excreted in breast milk [22]. Acute exposure to lindane during scabies treatment has potentiated seizures in people on medication that reduces the seizure threshold [23,24]. Lindane appears to be contraindicated for those undergoing therapy for human immunodeficiency virus (HIV) infection [23], attention deficit hyperactivity disorder using amphetamine [24], and in those who suffer from epileptiform seizures. Concern has been expressed that lindane may be a risk factor for the triggering of seizures in epileptics, as it may alter liver cell function. Lindane does cause oxidative stress, but does not appear to modify liver microsomal function, and in experimental systems these effects were mitigated by prior treatment with phenobarbital [25,26]. Consequently, those being treated with barbiturates may be at lower risk of suffering side effects from lindane. However, it is not clear whether people receiving anticonvulsant drugs in general are at greater risk of having seizures if exposed to lindane.

Various studies have shown that the solvent vehicle plays an important role in the rate of transdermal absorption of lindane [27,28]. In addition, much of the drug can also be absorbed while the treatment is being washed off, because a depot of lindane builds up in the stratum corneum [28–30]. In many countries, and several of the studies reported here, scabicides are still applied after a hot bath, but the resultant peripheral vasodilation is likely to enhance transdermal absorption. A related increase in the passage of lindane through the dermis has been identified if soap and hot water are used to remove the acaricide at the end of the treatment process.



Absorption can be minimized if cool water alone is used to remove residues of lindane products before bathing [30]. An investigation of the absorption of permethrin and lindane through human cadaver skin *in vitro* found that lindane achieved a rate of  $2\mu\text{g}/(\text{h cm}^2)$  in less than 5 h, whereas the rate for permethrin was one-tenth of this after 10 h. However, fresh guinea-pig skin absorbed both at the same rate [31].

Most RCTs have reported no serious adverse events using these topical insecticide-based products. One RCT reported five serious adverse events, two possibly associated with permethrin (rash and diarrhea) and three possibly associated with lindane use (pruritic rash, papules, and diarrhea) [13]. Postmarketing surveillance of permethrin use in the USA from 1990 to 1995 found six adverse events per 100 000 units of product (equivalent to one central nervous system adverse event for each 500 000 units of permethrin used) [32]. Case series based on community intervention studies have reported a burning paresthesia as one of the most frequent adverse events following permethrin use, particularly in the immunodeficient [32,33]. A burning sensation was the most frequent adverse event, although not significantly so, in the largest RCT, with 23 events in 233 people following application of 5% permethrin, compared with 12 of 232 after 1% lindane lotion ( $P = 0.08$ ) [13], and one case report has suggested that use of even small doses of lindane ( $60\mu\text{g}$  on the body followed by  $40\mu\text{g}$  on the head 6 days later) may have contributed towards the death of a 91-year-old patient treated for scabies [34].

### Comment

Generally, it is believed that all mites and their eggs are killed soon after treatment, although eggshells and scybala may persist for some time in the stratum corneum. Confirmation of cure is therefore difficult, because mites may not be detectable in posttreatment skin scrapings. It is impossible, therefore, to determine success until sufficient time has passed to permit the various lesions resulting from the infestation to heal. Many people show considerable improvement after 14 days, but a definitive clinical cure cannot be concluded until about 28 days after treatment, when all lesions present at the time of treatment should either be healed or resolving, without new lesions developing.

Five of the RCTs were conducted in developing countries. One other study was divided between the USA and Mexico [13], and two were from Italy [17,18]. It is not known whether scabies mites may be more susceptible to treatment in communities in which treatments are not generally available, but it is likely that prior exposure to acaricidal chemicals may select for reduced sensitivity in mites in developed countries, and some cases of suspected resistance, particularly to lindane, have been recorded [32,35].

### Implications for clinical practice

The evidence indicates that permethrin is more effective than crotamiton and lindane and it has been associated with fewer side effects than lindane. However, the high cost of permethrin may limit its use in some communities. Permethrin is probably more likely to be effective with one application than are other insecticides, but a second treatment may be necessary for all [36].

### Noninsecticide-based acaricides

#### Benefits

Randomized studies comparing the noninsecticide antiscabies agent crotamiton with insecticide-based treatments were described above.

We found one trial (158 adults and children) comparing 25% benzyl benzoate with sulfur ointment (concentration of sulfur not given) in a community study in India [37]. In this study, patients were first scrubbed in a bath; the treatments were then applied three times in 24 h (morning, night, and next morning). Assessments were made at approximately 5-day intervals. No significant difference was found between the treatments with regard to improvement of the lesions at 9–10 days – benzyl benzoate 68 of 89 (76%) versus 45 of 69 (65%) with sulfur. If lesions remained at this time, the patients were treated again, so that by 14–15 days there was improvement of symptoms in 81 of 89 patients (91%) in the benzyl benzoate group, in comparison with 67 of 69 (97%) for sulfur, which was also not significantly different. Another RCT conducted in Thailand (100 children aged 6 months–13 years) compared 10% sulfur ointment with 0.3% hexachlorocyclohexane (lindane) gel [38]. After 4 weeks of treatment, there was no significant difference between the treatments whether they were assessed using clinical signs (92% success for sulfur compared with 91% for lindane) or by parasitological findings (83% compared with 84% cure). However, the authors reported a significant difference ( $P < 0.05$ ) in adverse effects due to the foul odor following sulfur treatment.

Noncontrolled studies and case studies have indicated variable effectiveness for both benzyl benzoate (20% emulsion [39], 25% cream [40]) and sulfur ointment (5% [41], 6% [42], 10% [39,42], 2–8% [38]). The activity of these acaricides is related to the concentration of active drug in the vehicle and the number of times they are applied. In general, benzyl benzoate appears to require a minimum of two applications, and sulfur may require several applications over 1 week or longer [43,44].

We found a single RCT evaluated by the systematic review comparing pork fat containing 1% salicylic acid and cold cream as ointment vehicles for the delivery of sulfur [45]. The numbers in this study were small (51 confirmed cases), and differences in efficacy could have been due to chance effects. Every participant applied the sulfur ointment on three consecutive nights and then again 3 days later. Evaluations were made on the tenth day after the last treatment. This study is more relevant for the side effects observed, described below.

A recent RCT (110 children and adults, of whom 13 were drop-outs of some kind, not explained) compared three treatment regimens using either 8% (for children younger than 12) or 10% (for those over 12) sulfur ointment [46]. The method of randomization and the justification for using different concentrations were also not explained. Treatment was applied either once for 24 h or three times either on successive nights or on successive days, with bathing between treatments. Follow-ups were made at 14 and 28 days. Because original randomization allocations were not given, it is only possible to report the PP outcomes, which were cure (undefined) in only 14 of 33 people (42.4%) receiving a single application of sulfur compared with 29 of 32 (90.6%) applying the preparation on three successive nights or 31 of 32 (96.9%) applying on three successive days. The difference between a single and three applications was highly significant ( $P < 0.0005$ ), although the authors suggested significance of as much as  $P = 0.00000011$ . In this study, dermatitis side effects induced by the sulfur were reported in four cases (12.1%) following the single treatment regimen but eight (25%) and 11 (34.4%) cases following the two three-treatment regimens [46].

We found one study claiming randomization, without giving the method, that compared two products based on Nigerian plant extracts [47]. The authors state that they were “produced from

herbs that have acclaimed medicinal value.” However, the ingredient lists of the two preparations show nothing more than palm oil and shea butter as included plant derivatives. This study included scabies as one arm of an investigation of the two products against a variety of infections and involved 64 patients. The mean period of use to “clinical success” was 6.1 weeks using either Toto ointment, with 41/47 (87.2%), Toto soap 5/5 (100%), or both products together 12/12 (100%) success treatments.

Other noninsecticide active materials have only been described in nonrandomized studies and case series. One nonrandomized study comparing 5% sulfur ointment, 1% lindane cream, 25% benzyl benzoate cream, 10% crothamiton lotion, and 0.2% nitrofurazone in a water-soluble ointment found that nitrofurazone was the least effective, with a 70% cure rate [40]. A case series of 20 patients using the same nitrofurazone ointment produced “complete clinical cure” in 80% of cases [48].

Monosulfiram (sulfiram) is now mainly used only as a soap in resource-poor countries. Most studies are of poor quality and more than 50 years old, and more recent case studies show a high incidence of side effects (see Drawbacks section). Thiabendazole has been used as a 5% and a 10% cream applied over several days. In one case series, five of 19 patients (26%) were still infested after 5% cream was used twice daily for 5 days. The remaining patients were cured after a further 5 days of treatment [49]. Another case series, in which 10% cream was used, achieved an 80% success rate after 5 days [50].

### Drawbacks

Generally, studies have reported “only minor adverse reactions” for noninsecticide treatments for scabies. Most of these have been related to skin irritation or dermatitis, often following repeated or multiple applications of the formulation. The RCTs comparing vehicles or treatment regimens for sulfur ointment [45,46] did not provide adequate data for a full analysis of effects. Side effects were reported in patients and close contacts within 6 days of first being treated with either cold cream or pork fat with 1% salicylic acid: pruritus (31% vs 60%), xerosis (24% vs 34%), burning sensation (12% vs 17%), erythema (10% vs 2%), and keratosis (2% vs 15%) [45]. Where sulfur is used in developed countries, it is normally applied in petroleum jelly, and similar skin reactions have been reported as side effects in trials, case studies, and series [44,46,51]. Similar irritant reactions occur with repeat treatments using benzyl benzoate, particularly if naturally derived rather than synthetic material is used [44,52]. In one RCT, approximately 25% of people reported an increase in pruritus and dermatitis after treatment with two applications of 10% benzyl benzoate [53].

Monosulfiram in an alcohol vehicle has been associated with a systemic adverse event in a number of case reports in which the patients developed dermal edema, flushing, sweating, and tachycardia, especially after ingesting alcohol within 24 h of treatment [54–56]. This reaction occurs because monosulfiram is chemically related to disulfiram, used in the treatment of alcoholism (Antabuse). We could find no similar reports related to use of monosulfiram soaps.

Multiple applications of crothamiton can result in dermatitis, and there is one report of a suspected link with methemoglobinemia [20,44,57].

### Comments

Most studies in this group are not comparable owing to differences in the formulations used, in the concentrations of the active substances, and in the duration or number of applications. Evidence

for activity is limited in each case, and it is possible that some of the effectiveness is partially related to a physical effect – for example, sulfur in a heavy greasy base may physically trap and subsequently remove developmental stages of the mite from the skin surface, as would repeated use of ointment containing palm oil and shea butter. The mode of action of crothamiton is not understood, and there is doubt about both its acaricidal and antipruritic activities. Similar questions may apply to all of the noninsecticide-based treatments. The fact that these treatments are inexpensive means that they are more likely to be used in resource-poor and developing countries, where source materials may be less well characterized. Most of these compounds have been in use for around 50 years, and there is suspicion that resistance is developing in some areas [20].

### Implications for clinical practice

All of these products are likely to require two to four applications and are not particularly cosmetic. They may, therefore, suffer from compliance problems – for example, sulfur has a particularly unpleasant odor. However, the low cost and relative safety, apart from skin irritancy, make noninsecticide-based acaricides attractive alternatives to insecticide-based products where mites may have developed resistance or if cost is an issue.

### How successful are oral treatments for scabies? Would an oral treatment be suitable for treating an 82-year-old resident in a nursing home?

#### Orally administered treatments

##### Benefits

We found one systematic review examining eight RCTs of variable size and quality, one of which had inadequate follow-up. A placebo-controlled RCT (including 55 adults and children) found that significantly more people (23 of 29; 79%) treated with ivermectin, 200 µg/kg, were free from symptoms at 7 days, in comparison with two of 26 (8%) treated with placebo. The code was then broken and the controls and all patients who had not improved received ivermectin [58]. A comparative RCT (44 people) found no significant difference at 30 days in improvement of lesions between ivermectin 100 µg/kg (16 of 23; 70%) and benzyl benzoate 10%, applied twice over 2 days (10 of 21; 48%) [53].

It also evaluated one RCT (including 85 patients) comparing ivermectin 200 µg/kg with 5% permethrin cream, evaluated at 1, 2, 4, and 8 weeks [59]. In this study, a single dose of ivermectin relieved symptoms in 28 of 40 patients (70%), which was significantly fewer than permethrin (44 of 45; 98%). However, when a second dose of treatment was given after 2 weeks, there was no significant difference in the improvement rate between the ivermectin group (38 of 40; 95%) and the permethrin group, in which everyone was cured.

We found three new RCT reports published since the systematic review that compared ivermectin with permethrin. The first, from Pakistan (100 patients, with 14 lost to follow-up), compared a single dose of ivermectin 200 µg/kg with one 12-h application of 5% permethrin cream [60]. Parasitological examinations were performed and photographs taken at the commencement and after 4 weeks, with an interim examination at 2 weeks. At 2 weeks, 24/44 (54.5%) in the ivermectin group appeared cured, as did 20/42 (47.6%) treated with permethrin. Those not cured were treated again, so that at the fourth week 35/44 (79.5%) receiving ivermectin were cured compared with 37/42 (88.1%) receiving permethrin, showing no significant difference whether by ITT or PP analysis. There was

a significant difference in adverse events, with one patient having burning paresthesia in the permethrin group but seven events in the ivermectin group (four severe itch, three secondary bacterial infection, one headache) ( $P = 0.05$ ).

Another study in Pakistan (120 patients, all of whom completed the study) compared 200 µg/kg with 5% permethrin lotion (details of formulation not given) applied once for 10–12 h [61]. Infestation was confirmed by microscopy in about one-third of patients, and photographs were taken on days 0 and 14. Follow-up examinations were at 7 and 14 days. Efficacy was estimated on a graded scale, but cure at 7 days was reported as 41/60 (68.3%) for ivermectin and 44/60 (73.4% [*sic*]) for permethrin. However, by 14 days the cure rate was reported as 40/60 (66.7%) for both treatments. In addition to “cure,” the treatments were reported as “very effective” in a further 25% for permethrin and 20% for ivermectin.

A double-blind RCT from India (120 patients, three lost to follow-up) also compared ivermectin (two treatment regimens) with permethrin [62]. More than 70% of participants had infestation confirmed parasitologically by skin scraping and were followed up 7, 14, and 28 days after initial treatment. Treatments were: (i) ivermectin 200 µg/kg given once on day 1, together with a placebo cream, followed by placebo tablets (vitamin B-complex) on day 15; (ii) ivermectin 200 µg/kg given twice on days 1 and 15, with placebo cream on day 1; (iii) 5% permethrin cream on day 1, with placebo tablets on days 1 and 15. Cure was defined as 50% or more improvement in number of lesions, pruritus, and negative microscopy. Outcomes at 7, 14, and 28 days were 29/40 (72.5%), 38/40 (95%), and 36/40 (90%), respectively, for the single-dose ivermectin regimen and 29/40 (72.5%), 36/39 (92.3%), and 36/39 (92.3% PP, 90% ITT), respectively, for the double-dose ivermectin regimen. In contrast, the permethrin treatment gave a more rapid response, with 37/40 (92.5%) at 7 days, followed by 37/38 (97.4%) and 38/38 (100% PP, 95% ITT) after 28 days. These differences were not statistically significant [62].

A more complex RCT from India (103 patients, 23 lost to follow-up) divided between three treatments: ivermectin 200 µg/kg in a single dose, 25% benzyl benzoate lotion applied twice overnight on two consecutive nights, and 5% permethrin cream applied once [63]. Follow-ups were made at 7 and 14 days after treatment. If patients were not cured at 7 days they were retreated, but the results at 7 days were not reported. At 2 weeks posttreatment only PP analyses were given for the outcomes of 27/27 (100% PP, 79.4% ITT) cured (defined as no new lesions) for ivermectin, 27/28 (96.4% PP, 79.4% ITT) for permethrin, and 23/25 (92% PP, 65.7% ITT) for benzyl benzoate. The majority of the report was actually devoted to the economics of treatment, which concluded that, despite its low efficacy, benzyl benzoate was the most cost-effective product.

A similarly complex RCT from Senegal (181 patients, 22 lost to follow-up) used a skewed randomization to compare a single dose of ivermectin 150–200 µg/kg, taken on an empty stomach (68 patients), with a single 24-h application of benzyl benzoate 12.5% (65 patients), or two applications of benzyl benzoate separated by 24 h (48 patients) [64]. Follow-ups were conducted at 7, 14, and 28 days primarily using clinical diagnostic criteria. A retreatment at 7 days was considered necessary for seven patients in the ivermectin group, but none in either of the benzyl benzoate groups required a second treatment. Analyses were given ITT at 14 and 28 days as follows: ivermectin cure rates 16/54 (24.6%) and 28/65 (43.1%); benzyl benzoate applied once gave 37/65 (56.9%) at 14 days and 52/68 (76.5%) at 28 days, whereas respective outcomes for the double treatment with benzyl benzoate were 33/48 (68.8%) and

46/48 (95.8%). Both benzyl benzoate outcomes were highly significantly ( $P = 0.00008$  and  $P < 10^{-5}$ ) better than ivermectin. In this study, 30 patients experienced a dermatitis reaction to benzyl benzoate and seven had either abdominal pain (five) or diarrhea (two) following ivermectin treatment. This study was planned to recruit 400 patients, but because ivermectin proved so ineffective and showed a significantly higher risk of superinfection the study was terminated early for ethical reasons [64].

A relatively small RCT (53 patients, 43 of whom completed the study) found that ivermectin 150–200 µg/kg was statistically equivalent to 1% lindane lotion [65]. After 15 days, 14 of 19 patients (74%) had improved with ivermectin, in comparison with 13 of 24 (46%) treated with lindane. At 29 days, all but one of the remaining accessible patients in each group were cured – 18 of 19 (95%) with ivermectin versus 23 of 24 (96%) with lindane.

A large RCT conducted in India (including 200 patients) compared ivermectin 200 µg/kg with 1% lindane lotion applied overnight [66]. Assessments were made at 48 h, 2 weeks, and 4 weeks after treatment. After 4 weeks, 82.6% of the ivermectin group showed marked improvement, based on a clinical assessment, in comparison with 44.4% of those treated with lindane. The only adverse event of note was a severe headache in one person treated using ivermectin. Another RCT (110 children aged 6 months–14 years at the start of the study) conducted in Vanuatu compared a single dose of oral ivermectin 200 µg/kg with one application of 10% benzyl benzoate emulsion [67]. After 3 weeks, an assessment was made using clinical diagnostic criteria, in which 24 of 43 of the ivermectin-treated patients (54%) were considered cured, in comparison with 19 of 37 of those receiving benzyl benzoate (51%). This difference was not significant, but benzyl benzoate was significantly more likely to induce adverse skin reactions ( $P = 0.004$ ; odds ratio, 6.4, 95% CI, 1.6–25.0). However, this study suffered from a drop-out rate of 27% (30 of 110), which was not adequately explained by the authors.

An observational cohort study (six families, 12 adults and 20 children aged 1–10 years) used a 1% solution of ivermectin in propylene glycol to give a total dose of 400 µg/kg, applied twice with an interval of 1 week [68]. Evaluation was made on the basis of clinical evidence at 2, 4, and 6 weeks. All of the patients were cured without side effects or relapse.

### Drawbacks

Most of the RCTs were too small or too complex to provide adequate safety data for the use of ivermectin against scabies, particularly in children. What comment there is about adverse experiences is often inadequate, as most authors who report adverse events at all generalize comments to stating that adverse experiences “were mild” or treatments were “well tolerated”; such comments are wholly meaningless and no guide to what might be expected in clinical use. Ivermectin has been used extensively in community control programs for onchocerciasis and filariasis, and there have been few reports of serious adverse events [69,70]. There has been one report of a significant increase in the mortality rate in a psychogeriatric unit – 15 of 42 (36%;  $P = 0.001$ ) within 6 months of ivermectin use, in comparison with controls in the same care facility over a 3-year period [71]. However, each resident in the unit had previously received several applications of other scabies treatments, including lindane and permethrin. Use of ivermectin in the elderly in other countries has not resulted in any similar increase in mortality [72,73].



### Comment

Ivermectin has not yet been widely licensed for use against scabies. However, its use on a named-patient basis has become widespread as a component of treatment for hyperkeratotic scabies, in which it is often difficult to kill all the mites due to the limited penetration of the plaques (Figure 51.2) by topical acaricides. In this condition, ivermectin can reach trophic mites by incorporation into the living cell layer on which the mites feed. However, ivermectin is unlikely to have any direct effect on mite eggs, and failures of treatment have been reported unless either dosing is repeated or a topical scabicide is used concurrently [74–76]. So far, no proper dosing studies using ivermectin have been performed, and the relative underdosing using both ivermectin and benzyl benzoate in one study indicates how important a contribution to knowledge this would be [53]. Apart from drug dose level, timing of dosing with ivermectin is no doubt important in relation to efficacy. Of the newer studies, three gave no information on timing [60,61,63], one advised “before breakfast” [62], and one advised “on an empty stomach” [64], which would potentially have reduced the effective dose levels because the manufacturer suggests bioavailability is improved if the drug is taken with fatty food [76]. Furthermore, the borderline dose level of 150–200 µg/kg used in the Dakar study [64], combined with taking on an empty stomach, could have reduced uptake levels below an effectiveness threshold. However, it should also be noted that ivermectin had been used in Senegal in mass treatment programs for elimination of onchocerciasis for nearly 20 years prior to this evaluation of the drug for scabies, which could have selected for resistance in the mites. Similar repeated exposures using ivermectin in northern Australia for scabies control has resulted in selection of resistance there, and resistance to ivermectin as well as permethrin, the most widely used acaricide, will no doubt spread [77,78].

### Implications for clinical practice

A reliable and safe oral treatment is an attractive option for dosing and compliance with scabies treatment. However, ivermectin has still not yet been evaluated sufficiently to determine the most appropriate dosing regimen. It is likely it will never replace topical treatments, but used correctly it can be a useful adjunct to conventional treatment approaches.



**Figure 51.2** Hyperkeratotic crusts may develop in abnormal sites. (Reproduced with permission of the Institute of Dermatology, King's College Hospital, London.)

### Additional comment

The evidence for the effectiveness of all scabies treatments is still largely rudimentary, and the majority of studies have employed inadequate criteria for diagnosis and evaluation of efficacy. It is almost impossible to compare most studies, even when they are sponsored by the same organization, as almost every trial employs a different protocol and set of criteria for making the initial diagnosis, follow-up diagnoses, treatment regimen, and evaluation of success. The majority of studies have been conducted in developing countries, where scabies is not only more highly endemic than in western Europe or North America, but in many cases is also less likely to have been subjected to any form of therapeutic intervention. As a result, treatments should exhibit exemplary activity against these chemically naive mites. However, the most worrying aspect of reading the study reports is that, even in circumstances in which resistance to treatment cannot be an issue, the treatments of all types exhibit a disturbing lack of efficacy in the absence of retreatment and in some cases multiple retreatments. What evidence exists indicates that none of the topical products is reliable with a single application, and this picture may be further confused by the possibility that resistance to conventional neurotoxic compounds may have developed in some communities. The limited evidence available for oral ivermectin is far from the aspirations expressed by those dealing with problems of long-term infestation, and there is now evidence that in some regions the mites are no longer fully sensitive to ivermectin and in many cases are developing tolerance already. Consequently, further investigation is required for this and other neurotoxic insecticide treatments – first, to determine adequate drug regimens and reliable methods of evaluating them and, second, to confirm the susceptibility of the mites to those treatment compounds in all geographic zones.

### Key points

- Permethrin is probably effective in scabies treatment. Lindane has been withdrawn from most markets and has a higher potential for toxicity. Synergized pyrethrins may be effective, but more evidence is required and there is insufficient evidence that malathion shows activity.
- Crotamiton, benzyl benzoate, and sulfur show insufficient evidence of efficacy, as do nitrofurazone, monosulfiram, and thiabendazole.
- There is currently insufficient evidence of the effectiveness of ivermectin. Most studies have been small trials and larger studies have suffered high drop-out rates. Case studies indicate that ivermectin may be effective if used with a topical agent. A proper dose regimen evaluation is required. However, there is now evidence of resistance in some localities.

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## CHAPTER 52

# Head lice

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## Background

### Definition

Head lice (*Pediculus capitis*) are blood-feeding insects that are obligate ectoparasites of socially active humans. All stages of the life cycle infest the scalp, where the adult insects attach their eggs to the hair shafts. The juvenile forms (nymphs) are essentially miniature versions of adults, and there is no distinct larval stage.

### Incidence/prevalence

We found no data on the incidence and few recent published prevalence data from developed countries. Anecdote suggests that the prevalence increased in most communities in Europe, the USA, and other developed countries during the 1990s. One study in Belgium found a prevalence of up to 19.5% in some schools, and in a follow-up investigation of 6169 children (2.5–12 years) there was an overall prevalence of 8.9% [1,2]. A more recent study in Norway, where overall prevalence was low (1.63%), suggested that population density of the community and the age of the eldest child attending elementary school were the most significant factors influencing risk of infestation [3]. In one study, low socioeconomic status was a significant risk for the presence of infestation and an inability to treat these effectively [2].

### Etiology/risk factors

Observational studies indicate that infestations occur most frequently in schoolchildren, although there is no evidence of a link with school attendance. We found no evidence that either hygiene or hairstyle influences the risk, or that lice prefer clean hair to dirty hair.

### Prognosis

This infestation is essentially harmless. However, the stigma associated with head lice and the psychological trauma experienced by some people in their efforts to eliminate the infection greatly outweigh the physical impact of the infestation. Sensitization reactions to louse saliva and feces may cause local irritation and erythema. Secondary infection of scratches may occur. Lice have been identified as primary mechanical vectors of scalp pyoderma caused by streptococci and staphylococci usually found on the skin [4].

### Diagnosis

Only finding living lice on the scalp can confirm a diagnosis of active infestation (Figure 52.1). Eggs glued to hairs, whether hatched (nits) or unhatched, are not proof of active infection, because dead eggs may appear viable for weeks. Itching, resulting from multiple bites, is not diagnostic, but may increase the index of suspicion. Combing is a more effective diagnostic method than visual inspection of the hair [5–8].

### Aims of treatment

The aim of treatment is to eliminate infestation by killing or removing all head lice and preventing their eggs from hatching.

### Outcomes

Treatment success is given as the percentage of people completely cleared of head lice. There are no standard criteria for judging treatment success, although guidelines have recently been published [9]. Many trials have used different methods, and often the method was not stated. Few studies are pragmatic.

### Method of search

- The Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine performed the initial search for a systematic review compiled in July 1998, updated in February 2001 and July 2006; search date March 2006; primary sources: Cochrane Central Register of Controlled Trials, Medline, Embase, Bath Information and Data Services (BIDS SC), BioScience Information Service (BIOSIS), and Toxicology Literature Online (Toxline).
- Medline update search for evidence-based dermatology, May 2012.
- Google Scholar search, June 2012.
- Manual searching of relevant journals.

### Context

Selection of studies for inclusion is based primarily on their status as randomized, controlled, trials with adequate reporting, randomization, and follow-up. However, an additional factor, not normally taken into account, is the context and timing of the studies. For example, does a study conducted in a closed environment such as

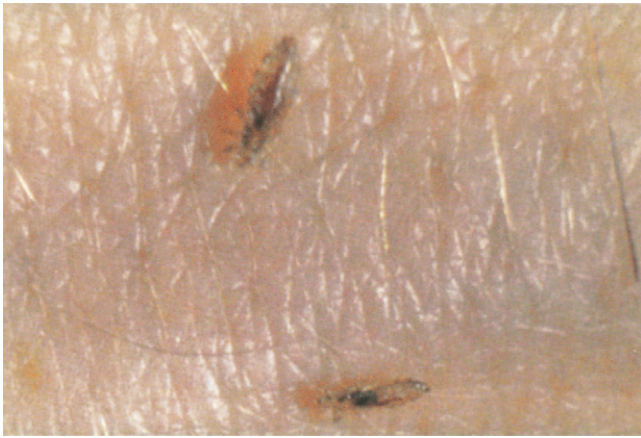


Figure 52.1 Head lice are difficult to see against human skin.

a boarding school or an isolated island community have the same weight as a study conducted in the wider community where participants are likely to have multiple encounters with other potentially infested people during the course of the study? One way in which investigators have attempted to address this question is to report the background prevalence of infestation in the community. However, as far as can be determined, these data have never been used in any informative way to evaluate the outcome data, so reporting of prevalence seems to exist in a contextual vacuum.

The second factor that must be considered is the age of the study. Does the outcome of an investigation performed 30 years ago, using a newly introduced active substance, carry the same weight now as a study performed within the last 2–3 years? Obviously the value depends upon where the studies were conducted and how much the particular material has been used in the geographical region in the past. This is particularly important when considering the value of studies sponsored by the pharmaceutical industry because they are more likely to compare a “new” material with something that may have been used for many years and can thereby demonstrate superiority because the old material is now affected by resistance or vigor tolerance. This practice is not necessarily an indication of bias because there may be good therapeutic reasons for demonstrating that an established treatment favored as an “old friend” by prescribers should no longer be employed. However, the justification for using such a product comparison should be considered.

## Questions

### How successful are treatments for head lice?

#### Case scenario 52.1

A 10-year-old girl with shoulder-length hair is diagnosed with head louse infestation. How easy would it be to treat her?

#### Insecticide-based pharmaceutical products

**Efficacy** We found two systematic reviews [10,11]. The first (search date March 1995; seven randomized controlled trials, 1808 people), of 11 insecticide products, included lindane, carbaryl, malathion, permethrin, and other pyrethroids in various vehicles [11]. Two randomized controlled trials (RCTs) were selected as showing that only permethrin produced clinically significant differences in the rate of treatment success. Both compared lindane (1% shampoo)

with permethrin (1% crème rinse) [12,13]. In that analysis, permethrin was found to be more effective than lindane.

The first Cochrane systematic review (search date May 1998, updated February 2001) set stricter criteria for RCTs and rejected all but four trials [10]. It initially excluded both studies on which the earlier review was based. The most recent update of Cochrane (July 2006, now withdrawn), in attempting to address criticisms of the 2001 publication, evaluated a wider range of studies in greater detail. No clear therapeutic guidelines were obtained from the analyses, as it was impossible to draw up-to-date conclusions from the widely differing results obtained using different formulations of the same materials, different treatment regimens, and different assessment criteria, at different times, especially where resistance to insecticides has had an impact on some of the better-designed trials. A new Cochrane review is at the protocol stage [14].

One RCT (193 schoolchildren) compared malathion (0.5% alcoholic lotion) with *d*-phenothrin (0.3% lotion – no longer available in many countries), both applied for 8 h or overnight. One day after treatment, fewer people treated with malathion had lice – eight of 95 (8%) versus 59 of 98 (60%) treated with phenothrin. This difference had increased by day 7 – six of 95 (6%) versus 60 of 98 (61%). However, some children not free from lice on day 1 had become louse free by day 7 in both groups, suggesting that some parental intervention had influenced the results, but no further follow-ups were performed [15]. One RCT (66 people) compared 0.5% malathion (alcoholic lotion applied for 20 min) with 1% permethrin (crème rinse applied for 10 min). One application was used, but a second treatment was given if lice were found after 7 days. At day 7, 33 of 41 people (80%) treated with malathion were louse-free, as were 13 of 22 (59%) treated with permethrin. After the second treatment, the overall cure rate at day 14 was 40 of 41 for malathion (98%) and 15 of 22 (68%) for permethrin [16].

We found one report describing two multicenter, double-blind RCTs comparing effectiveness of 0.5% ivermectin lotion with the product vehicle. Data from the two studies were combined for the effectiveness analysis of the 289 enrolled youngest family members. A further 781 family members took part in a safety analysis. A single 10 min treatment evaluated 14 days later showed 104 children from 141 (73.8%) were louse free throughout the period after treatment compared with 26 of the 148 (17.6%) receiving the vehicle placebo [17].

We found another report of two multicenter RCTs that compared 0.9% spinosad crème rinse, without nit combing, and 1% permethrin crème rinse plus nit combing. Both products were applied for 10 min, with a repeat after 7 days if lice were present. In the first RCT, households were randomized and all members of the household treated. Ninety-one households (243 patients) were allocated spinosad and 89 households (256 patients) received permethrin. In the second RCT, 83 households (203 people) were treated with spinosad or 84 households (214 people) were given permethrin. Analysis of outcome was measured in the youngest household member (180 children in the first RCT and 167 in the second RCT) who were lice free at 14 days after the last treatment. Absolute outcomes were not clear because they were given as percentages, with 84.6% success for spinosad and 44.9% for permethrin in the first study and 86.7% and 42.9% respectively in the second trial [18].

**Drawbacks** Only minor adverse effects have been reported for most insecticides. The exception is lindane, which has been withdrawn from use in nearly all developed countries and for which



there are extensive reports of effects related to overdosing (treatment of scabies), and absorption (treatment of head lice). Lindane passes transdermally during treatment of head lice [19], and a specific review has now summarized all case histories of adverse events resulting from its use in this application [20].

We found no confirmed reports of adverse effects from therapeutic exposure to the organophosphorus compound malathion. A randomized, open, volunteer study (32 people) examined transdermal absorption of malathion from four head louse treatment products formerly available in the UK [21]. Urinalysis for malathion metabolites found that 0.2–3.2% of the applied dose was eliminated in urine, before decreasing to baseline values by 96 h. Erythrocyte cholinesterase levels were clinically unaffected, irrespective of dose or whether the skin was excoriated.

Pyrethroid insecticides are listed as contraindicated for people with ragweed allergy, but we found only one report of an anaphylactoid reaction to a head louse treatment product [22].

**Comments** Follow-up for 7 days is inadequate, because louse eggs normally take at least 7 days to hatch. A second application of insecticide should be given 7–10 days after the first treatment. The primary end point of a study is absence of infestation at least 14 days after first treatment.

No RCT has yet evaluated the effect of formulation vehicle activity. Studies *in vitro* suggest that excipients of products (e.g., terpenoids and solvents) may have contributed significantly to pediculicide activity, in some cases more than the insecticide itself [23].

Resistance to one or more insecticides has now been identified in most developed countries. There are no data on the prevalence of resistance. However, resistance to pyrethroids (permethrin, *d*-phenothrin, and natural pyrethrum) is widespread in Europe, North America, and Australia, and malathion resistance is present in Europe and Australia [24–29].

**Implications for practice** Evidence for efficacy of any older insecticide-based pediculicide is now extremely limited. Early commercial support for permethrin produced a greater body of evidence of its efficacy. However, all older insecticides still in use are affected by resistance, which varies considerably both within and between countries. Available data are insufficient to judge this factor other than on a case-by-case basis, but more recent studies conducted to evaluate noninsecticide products and using insecticides as comparators are probably a good indication of the impact of resistance on communities. The newer insecticides ivermectin and spinosad are not affected by resistance, and are still relatively less widely used than older materials, which would reduce the risk. However, it is possible that resistance will appear in head lice in the future, and users should be conscious of this possibility. In cases of treatment failure, where resistance is indicated by finding all stages of lice soon after treatment, an alternative treatment approach – for example, physical removal, physically disrupting insecticide, or herbal material – would be more appropriate.

#### **Physically disrupting insecticides**

**Efficacy** We found one RCT (253 children and adults) conducted in the UK comparing 4% dimeticone lotion (4% high molecular weight dimeticone in a cyclomethicone solvent) with 0.5% *d*-phenothrin aqueous liquid (no longer available in any country). Both products were applied overnight using two applications 7 days apart, with follow-ups on days 2, 6, 9, and 14. At 14 days, no sig-

nificant difference was found between the numbers of individuals free of lice with phenothrin liquid (94/125, 75%) or with dimeticone lotion (89/127, 70%) [30].

A second RCT (58 children and 15 adults) in the UK compared the same 4% dimeticone lotion with 0.5% malathion aqueous emulsion (no longer available in any country) [31]. In this study also, followed up on four occasions, both products were applied overnight and reapplied after 7 days. Cure of infestation was defined as no evidence of head lice after the second treatment, and particularly by day 14. Some people were found free from lice but later were reinfested. Worst case, intention-to-treat (ITT), analysis found dimeticone was significantly more effective than malathion, with 30 of 43 (69.8%) participants cured using dimeticone compared with 10 from 30 (33.3%) using malathion ( $P < 0.01$ , relative risk [RR], 2.09; 95% confidence interval [CI], 1.21–3.60). Per-protocol analysis showed cure rates of 30/39 (76.9%) and 10/29 (34.5%) respectively.

An RCT conducted in Turkey (72 school children) compared 4% dimeticone lotion with an alternative formulation, both products applied overnight on two occasions a week apart [32]. The ITT analysis showed 35 of 36 (patients treated with the commercial lotion had no lice after the second treatment but there were two protocol violators, giving 91.7% treatment success. The alternative product gave 30/36 (83.3%) treatment success, a difference of 8.4% (95% CI, –9.8 to +26.2%). The cure rates per-protocol were 33/34 (97.1%) and 30/35 (85.7%) respectively.

We also found an RCT conducted in Brazil (145 children 5–15 years) comparing a different dimeticone lotion (92% mixture of low molecular weight dimeticones with triglycerides, jojoba wax, and terpenoids) with 1% permethrin lotion [33]. Treatments were applied overnight and reapplied after 7 days, but follow-up was only conducted for 9 days. During the study, children were isolated in a holiday camp to avoid reinfestation from contacts in the community. Assessments on day 9 showed no lice present in the dimeticone group on 70 of 72 children (97.2%) compared with 48 of 71 (67.6%) in the permethrin group. This per-protocol analysis gave a significant advantage to dimeticone ( $P < 0.001$ , RR, 1.44; 95% CI, 1.22–1.70). One participant was lost from each group, which would have given an ITT outcome of 95.9% success for dimeticone and 66.7% for permethrin.

We found one RCT (60 people, eight drop outs) conducted in the USA that compared 50–50 isopropyl myristate–cyclomethicone (IPM-C) with 0.33% pyrethrum shampoo synergized with 4% piperonyl butoxide; both products were applied for 10 min [34]. IPM-C was applied on up to three occasions a week apart, depending on whether lice were present at an assessment. Pyrethrum shampoo was applied on two occasions a week apart. This study was exceptionally difficult to interpret because primary outcome data were given as percentages and presented graphically and there was no consistency of treatment regimen – every time a patient was found with lice they were treated again, but several missed interim visits. However, the authors stated that 52% of patients treated with IPM-C were louse free at day 21 which was significantly more effective compared with pyrethrum – values not given.

A second RCT of IPM-C (141 children and 27 adults), this time conducted in the UK, compared the product with 1% permethrin crème rinse, both products applied twice for 10 min with a week between [35]. By the 14th day after start of treatment, 91 patients out of 111 (82.0%) treated with IPM-C were louse free compared with 11 of 57 (19%) treated using permethrin ( $P < 0.001$ ; RR, 4.25; 95% CI, 2.48–7.28).

We found one report of two double-blind, multicenter, vehicle placebo-controlled RCTs investigating the activity of 5% benzyl alcohol and mineral oil emulsion (BA/MO) [36]. In both studies the treatments were applied twice, a week apart, and final follow-up was 14 days after the second application. In the first study (125 children), 48 of 63 treated using BA/MO were louse free at day 21 compared with three of 63 in the placebo group. In the second RCT, also of 125 children, the BA/MO preparation eliminated lice from 48 of the 64 patients compared with the 16 of 61 in the placebo group. Over all RCTs and open-label studies, 6.8% of patients treated with BA/MO reported application site discomfort.

We also found a report of one RCT comparison (42 adults and children) between a spray – with a named active of 1% sodium chloride (0.1709 M), with a benzyl alcohol excipient, left on for 24 h, – and a 1% permethrin crème rinse applied for 10 min. Each product was applied once, with a follow-up treatment 7 days later only if lice were found. After one drop out from each group the ITT analysis found 16 people of 21 (76.2%) with no lice in the sodium chloride group after 14 days and nine participants of 21 (42.9%) treated with permethrin (85.0 and 45.0% successful respectively per-protocol) [37]. How much of this activity was truly as a result of salt exposure and how much due to benzyl alcohol is not clear as the dose concentration of benzyl alcohol is not specified on the pack.

We have found another report of two RCTs evaluating 1,2-octanediol, a wetting agent [38]. In the first (520 children and adults) three-center study, a preparation of 1,2-octanediol in 20% isopropanol lotion was evaluated using two application times (2–2.5 h or overnight) in comparison with 0.5% malathion aqueous emulsion. In this study, 1,2-octanediol lotion was significantly ( $P < 0.0005$ ) more effective with successful elimination of lice for 124 of 175 (70.9%) of patients receiving the 2–2.5 h treatment (RR, compared with malathion, 1.50; 95% CI, 1.22–1.85), and when 1,2-octanediol was applied overnight the success rate was 153 of 174 (87.9%) (RR, 1.86; 95% CI, 1.54–2.26) compared with 81 of 171 (47.4%) patients with malathion. The second study (121 children and adults), conducted in two centers, compared the 1,2-octanediol–20% isopropanol lotion, 2–2.5 h with a 1,2-octanediol alcohol-free mousse applied for either 2–2.5 h or for 8 h/overnight. The mousse applied for 8 h/overnight cured 31 of the 40 (77.5%) patients, compared with 24 of the 40 (60.0%) treated using the alcoholic lotion (RR, 1.29; 95% CI, 0.95–1.75; number needed to treat, 5.7) but when the mousse was applied for 2–2.5 h, only 17 from 41 (41.5%) patients were cured (RR, 0.69; 95% CI, 0.44–1.08) compared with the lotion. However, irritant application site adverse events were more common using 1,2-octanediol in the alcoholic lotion at both 2–2.5 h (12.0%,  $P = 0.001$ ) and 8 h/overnight (14.9%,  $P < 0.0005$ ), compared with 0.5% malathion (2.3%). Similar reactions were also found when using the lotion for 2–2.5 h in comparison with the alcohol-free mousse ( $P < 0.045$ ).

We also found one cohort study (41 children) investigating the effect of a more viscous dimeticone preparation using 4% high molecular weight dimeticone in a nonvolatile liquid gel base applied for 15 min on two occasions a week apart [39]. This study found that all lice and their eggs were killed following the first application because no nymphs were observed at any of the four follow-up visits.

More recently we found one RCT (90 children and adults) in which the liquid gel formulation of 4% high molecular weight dimeticone was applied only once for 15 min compared with two applications 7 days apart of 1% permethrin crème rinse. The ITT

analysis found successful treatments in 30 people of 43 (69.8%) of the dimeticone group and seven of 47 (14.9%) in the permethrin group after 14 days ( $P < 0.001$ ; odds ratio [OR], 13.19; 95% CI, 4.69–37.07). The per-protocol outcome was similar, with 27 participants out of 35 (77.1%) cured for dimeticone versus seven of 45 (15.6%) for permethrin [40].

We found a report of one RCT (45 children and adults) that compared a spray containing 20% tocopheryl acetate in a cyclomethicone carrier, applied for 20 min, with 1% permethrin crème rinse, both products applied twice with 7 days between. After 14 days, 20% tocopheryl acetate was significantly ( $P = 0.033$ ) more effective than 1% permethrin, worst case analysis showing 13 successful treatments in 23 people (56.5%) compared with five successes from 22 (22.7%) for permethrin. After addressing anomalies of reinfestation within households, the underlying cure rate was 17 people from 23 (73.9%) for tocopheryl acetate compared with five from 22 (22.7%) (OR, 9.63; 95% CI, 2.46–37.68;  $P < 0.001$ ) [41].

**Drawbacks** We found no drawbacks for 4% dimeticone lotion. It was reported as producing fewer irritant reactions (three of 127 patients, 2%) versus phenothrin liquid (11 of 125, 9%) [27], none (0%) versus malathion (two of 30, 6.7%) [31], and none as a gel [39]. The mixed dimeticone preparation produced two irritant reactions in 73 patients (2.7%) compared with none for permethrin [33]. Similarly, IPM-C produced a low number of adverse events. In the US study, none were specifically reported beyond being “mild” [34]; in the UK study, six adverse events (5.4%) occurred compared with none for permethrin [35]. In all cases with this group of materials the product-related events were application site reactions such as dry skin or erythema, or ocular irritation if the fluid ran into the eyes [36,38–41].

**Comments** Dimeticone has been shown to have a physical mode of action in which it coats the insects, blocks the respiratory system, and disrupts their ability to manage water [42]. This mode of action circumvents resistance to conventional neurotoxic insecticides and is unlikely to be affected by resistance.

Since 2006 there have been numerous products released into the European markets based on silicones and other synthetic oils. At the time of writing, most of these have not been supported by peer reviewed reports, although a high proportion claims to be “clinically proven.”

**Implications for clinical practice** In several countries in Europe, physically disrupting insecticides have almost completely replaced conventional insecticides for louse control. Because they are not affected by the resistance mechanisms that render conventional insecticides ineffective and are not absorbed transdermally, physically disrupting insecticides offer the principal alternative method of treatment, especially for people concerned about using insecticides on safety grounds.

Most physically acting preparations require relatively small quantities for a thorough treatment, mean quantities quoted as around 60 mL. However, prescribing recommendations for BA/MO are for considerably greater quantities, up to 48 fluid ounces (1364 mL) for long hair. Such large volumes are not only difficult to manage physically but also highly costly per treatment.

#### **Antimicrobial and other oral treatments**

**Efficacy** We found one RCT (115 children) in which cotrimoxazole (trimethoprim and sulfamethoxazole), either alone (10 mg/kg per

day over 10 days) or in combination with 1% permethrin crème rinse, was compared with 1% permethrin crème rinse alone (one application, with a second after 7 days if lice remained) [43]. After 2 weeks, the number of children who were louse free with cotrimoxazole alone (28/36, 77.8%) did not significantly differ from the number with permethrin alone (28/39, 71.8%), but the combination treatment (37/40, 92.5%) was superior ( $P < 0.03$ ) to permethrin alone.

We also found one double-blind, double-dummy, RCT (812 patients, 15 lost to follow-up and a total of 35 (6.5%) not completing the study, randomized by the 376 households), conducted in the UK, Ireland, France, and Israel, comparing two doses of oral ivermectin at 400 µg/kg with 0.5% malathion alcoholic lotion, each given on days 0 and 7 [44]. Placebo tablets, given to malathion-treated patients, were identical in composition to those of ivermectin minus the active substance. Ivermectin-treated patients were treated using a placebo lotion of 100% isopropanol. In the ITT analysis, 378 of 397 (95.2%) patients receiving ivermectin were lice free on day 15 compared with 352 of the 414 (85.0%) receiving malathion (absolute difference [AD], 10.2%; 95% CI, 4.6–15.7;  $P < 0.001$ ). In the per-protocol population, 339 of 349 (97.1%) of those receiving ivermectin were lice free on day 15, whereas 327 of 364 (89.8%) patients treated with malathion had no lice (AD, 7%; 95% CI, 2.8–11.8;  $P = 0.002$ ). Patients from both groups who still had lice at day 15 (eight ivermectin, 31 malathion) were switched to the other treatment. At the 29th day all except one patient receiving ivermectin had been cured. In this study, seven of 398 patients (1.8%) receiving ivermectin and five of 414 (1.2%) on malathion withdrew as a result of adverse events. Two serious events occurred: one child receiving ivermectin had a seizure, subsequently diagnosed with a right rolandic (centrotemporal) focus, and another child on malathion was hospitalized as a precaution following a severe headache. Overall, there were 30 (7.5%) treatment-related events in the ivermectin group and 45 (10.9%) in the malathion group.

We found a smaller RCT (80 children), conducted in Egypt, comparing a single dose of either oral ivermectin 200 µg/kg or 0.5% malathion lotion, with a repeat treatment if required [45]. After the single dose, 31 of the 40 (77.5%) patients treated with ivermectin were louse free, as were 35 of the 40 (87.5%) treated with malathion. Following the second treatment dose, for those with lice at day 8, the success rates increased to 92.5% for ivermectin and 95% for malathion.

We found various cohort studies and nonrandomized studies of oral and related treatments. One cohort study (114 schoolchildren) in which cotrimoxazole (8 mg/kg daily over 12 days) plus 1% lindane shampoo applied for 10 min was compared with 1% lindane shampoo alone [46]. If lice were found after 2 weeks, a further treatment was given. No significant difference was found between the treatments at either examination. At 2 weeks, the louse-free rate with lindane shampoo was 53 of 69 (76.8%), compared with 39 of 45 (86.7%) for the combination treatment. The cure rate increased following the second treatment to 63 of 69 (91.3%) for lindane shampoo and 44 of 45 (97.8%) with the combined treatment. Other nonrandomized studies have investigated the activity of thiabendazole (20 mg/kg twice daily for 1 day, with repeat treatment after 10 days) [47], levamisole [48], and ivermectin (200 µg/kg) [49], each of which has shown variable results related to dosing.

**Drawbacks** The RCT comparing cotrimoxazole with permethrin reported three cases of scalp irritation with permethrin and nine

incidents of intense but transient pruritus following cotrimoxazole alone. Three children treated with cotrimoxazole developed allergic rash and were withdrawn, and three others experienced nausea and/or vomiting. Similar side effects have accompanied oral treatments using ivermectin and thiabendazole. In all oral treatment studies dosing may be critical because most of the active compounds are either metabolized rapidly or have relatively short half-lives due to rapid excretion [50]. Additionally, there is some evidence that these materials may have relatively short useful lives because in vitro it has been demonstrated that lice exposed to lower than optimal dosing, such as could occur if too little is given or lice arrive on the head after blood levels have started to decline, over-transcribes detoxification genes that are involved in tolerance/resistance [51].

**Comment** Cotrimoxazole is believed to eliminate the symbiotic microorganisms associated with the gut of lice, inhibiting their viability and development. However, its use is inappropriate for this condition, due to the relatively high risk of adverse reactions to the drug. In one RCT, for example, a quarter of children taking cotrimoxazole developed intense pruritus after 3–4 days, even though it disappeared after 1–3 h. Potentially serious, although rare, adverse effects associated with cotrimoxazole include Stevens–Johnson syndrome, erythema multiforme, and blood disorders.

**Implications for clinical practice** It is unlikely for any orally administered drug to be a first choice for treatment despite current problems with resistance, although it appears to be more acceptable in the USA than Europe. The large RCT comparing ivermectin and malathion conducted in Europe only considered use of the product on cases of infestation nonresponsive to other medications. The introduction of alternatives, such as physically disrupting insecticides and herbal products, is likely to make ivermectin, and especially cotrimoxazole, curious therapeutic anachronisms.

### **Mechanical removal of lice or viable eggs by combing**

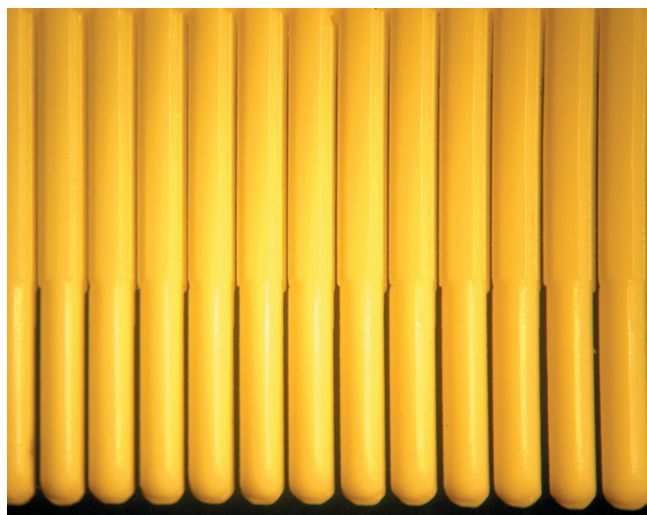
**Efficacy** We found one systematic review that evaluated louse removal by combing compared with insecticide treatment, but it did not evaluate nit combing to remove eggs. Three studies compared insecticide treatments with “wet combing with conditioner.” One study, a community-based pragmatic RCT (72 people) included in the Cochrane review, compared “bug-busting” (wet combing with conditioner) with two applications of 0.5% malathion alcoholic lotion 7 days apart [52]. Seven days after the second treatment (day 14), fewer people using malathion (nine of 40, 23%) had lice in comparison with those using “bug-busting” (20/32, 63%). A second small RCT, in which a trained hairdresser performed the first combing treatment or applied the insecticide product, compared a single application of permethrin (1% crème rinse) with “bug-busting” [5]. After 14 days, more people treated with permethrin still had lice (eight of 11 (73%) vs eight of 14 (57%)). We found one RCT (30 people) that compared 0.2% *d*-phenothrin lotion (no terpenoids in the vehicle) applied twice at an interval of 7 days, together with some level of combing (not clearly specified) versus “bug-busting” [53]. After 14 days, the cure rate with phenothrin lotion (two of 15, 15%) did not significantly differ from that with “bug-busting” (eight of 15, 53%). A more recent RCT (133 young people) compared “bug-busting” with insecticide treatment, divided between 0.5% aqueous malathion liquid and 1% permethrin crème rinse [54]. Nine of 70 individuals treated with insecticide – five of 30 (17%) with malathion and four of 40 (10%) with



permethrin – had no lice after 6 days, and 32 of 62 (52%) using “bug-busting” had no lice after 14 days. We found one RCT (95 adults and children) comparing combing with a metal nit/louse comb plus 1% permethrin crème rinse with permethrin alone [55]. Treatments were applied by a health-care professional. If lice were found after 7 days, an additional course of treatment (insecticide or insecticide plus combing) was given. There was no significant difference between the cure rates at 2, 8, and 15 days – louse-free patients at day 2: 49/59 (83%) without combing and 24/33 (73%) with combing; at day 8 before retreatment: 27/59 (46%) with no combing and 11/33 (33%) with combing; and at day 15: 47/60 (78%) without combing and 24/33 (73%) with combing.

We found three RCTs that evaluated different aspects of nit combing using “half-head” studies in which combs were randomly assigned so that one was used on one side of the head and another on the other side. The first RCT (30 children) compared nit combs from different manufacturers of insecticide treatments after using 1% permethrin crème rinse [56]. The combs were not significantly different for removing head lice, but one plastic comb with stepped teeth (Toppyc™, Johnson & Johnson, Brazil) (Figure 52.2) was significantly more effective ( $P = 0.0004$ ) at removing louse eggshells than the other two combs. A second RCT (27 children) conducted in Australia compared a metal pin comb (Licemeister™, National Pediculosis Association, USA) with a plastic comb (Lady Jayne, Richardson Sheffield, UK) after application of a viscous head louse treatment product. No difference was detected in comparing the combs for ability to remove lice, but the metal comb was significantly ( $P < 0.005$ ) better at removing hatched, dead, and live louse eggs [57]. The third RCT from Argentina (50 children) compared two plastic and two metal combs for removal of lice and louse eggs/nits without prior pediculicide use. The plastic combs were generally more efficient at removing lice, with the KSL® (KSL Consulting, Denmark) more efficient than NOPUCID® (ELEA S.A., Argentina), although only significantly ( $P < 0.007$ ) for third-stage nymphs. Comparison of the metal combs found the ASSY® (Assy, Argentina) more efficient on all stages than a KSL metal comb and significantly ( $P < 0.009$ ) at removing eggs of all types [58].

**Drawbacks** We found no evidence of drawbacks from combing alone, apart from discomfort for both the carer and the person



**Figure 52.2** A plastic comb with “stepped teeth,” which have been found to be more effective for removing nits and eggs.

being combed. Potential drawbacks exist for wet combing with conditioner. This requires conditioning crème rinses to be left on the scalp for prolonged periods, but adverse reactions to hair-conditioning agents have occurred after normal limited cosmetic use. Reactions include allergic contact dermatitis, urticaria, urticaria with systemic symptoms, and angioedema [59–63].

**Comment** All four studies comparing insecticide treatments with “bug-busting” were performed in areas in which resistance to the insecticide employed was either recognized before commencing the study or else identified as part of the study. As a result, the potential effectiveness of the insecticides was limited. We found a cohort trial that indicated that a conditioner-like formulation could be an effective pediculicide if allowed to dry on the hair [64]. A similar effect could occur with prolonged combing during “bug-busting.” Studies evaluating nit combing as an adjunct to insecticide treatment used combs that differed considerably in material and construction, so it was difficult to attribute efficacy, or lack of it, to either the pediculicide or the comb.

**Implications for clinical practice** Although combing may seem an attractive, simple, and safe treatment method, there is no real evidence that it is effective, especially when practiced by carers who may have little skill in the method. What little evidence is available indicates that insecticide-based products are more likely to be effective if applied twice with an interval of 1 week, even in areas in which insecticide resistance has developed. No doubt the success of currently used insecticides will diminish further with time, but combing requires better evidence of success before it will replace chemical treatments for the majority of patients.

#### **Herbal treatments and essential oils**

**Efficacy** We found one RCT conducted in Israel (143 children) that compared a spray based on coconut and anise (concentrations not given, product now withdrawn in most countries) with an insecticide spray containing a mixture of insecticides (0.5% permethrin, 0.25% malathion, synergized by 2% piperonyl butoxide, now withdrawn from most countries) [65]. Coconut and anise spray was applied three times at 5-day intervals and insecticide twice 10 days apart. There was no significant difference between the cure rate with the coconut and anise spray (60/70, 86%) and that with insecticide (59/73, 81%).

A second RCT (100 children and adults, with four withdrawals) conducted in the UK compared the same coconut and anise spray applied for 15 min with 0.43% permethrin alcoholic lotion applied for 45 min, both applied twice with 1 week between applications [66]. The spray was significantly more successful with 41 of 50 patients (82.0%) cured compared with 21 of 50 (42.0%) for permethrin ( $P < 0.0001$ ; AD, 40%; 95% CI, 22.5–57.5%). Per-protocol success rates were 40 of 48 (83.3%) and 21 of 48 (43.8%) respectively. Both products proved to be irritant, with 33 people reporting adverse reactions following alcohol contact with excoriated skin and respiratory irritation due to the oil of anise.

We found two RCTs evaluating the efficacy of tea tree oil (melaleuca oil). The first RCT conducted in Australia (132 school children of whom 123 were fully compliant) compared three products: an oily solution containing 10% tea tree oil and 1% lavender oil (TTO/LO) applied for 10 min on 3 days, each a week apart; an aqueous emulsion containing BA/MO also applied for 10 min on three occasions; and a mousse containing 0.165% pyrethrins and 1.65% piperonyl butoxide applied twice for 10 min [67]. Final



assessments were made 1 day after the final treatment for each product; that is, day 8 for the insecticide mousse and day 15 for the two other products. Louse-free outcomes for the ITT populations were 41 of 43 patients (95.4%) for TTO/LO, 40 of 45 (88.9%) for BA/MO, and 10 of 44 (22.7%) for the pyrethrin mousse. In the per-protocol analysis the respective outcomes were 40 of 41 (97.6%), 37 of 37 (100%), and 10 of 30 (33.3%). Both noninsecticide products were significantly ( $P < 0.001$ ) more effective. The TTO/LO product caused significantly ( $P < 0.001$ ) more adverse events, with 20 (46.5%) participants reporting stinging or drying effects at the application site compared with three (6.7%) for BA/MO and four (9.1%) for pyrethrin mousse.

The second RCT (92 children), also conducted in Australia, employed a novel approach to evaluation of ovicidal activity of products [68]. It compared a single application of each of three products: TTO/LO, an oily product containing 11% eucalyptus oil and 1% lemon tea tree oil (EO/LTTO), and BA/MO. After completion of the single application treatment, at least 10 viable louse eggs were removed from each participant and incubated in the laboratory to evaluate the ovicidal effect. Using generalized estimating equations it was found that the ovicidal effects of the three products were  $3.3 \pm 16\%$  for EO/LTTO,  $44.4 \pm 23\%$  for TTO/LO, and  $68.3 \pm 38\%$  for BA/MO. In this study, EO/LTTO caused stinging adverse events in 20% of the children compared with 12.9% treated with TTO/LO. No outcome data were given for the children who were treated.

Another Australian RCT (152 children, 39 noncompliant) compared EO/LTTO solution with 1% malathion shampoo and pyrethrin plus piperonyl butoxide mousse [69]. Both insecticide products were applied twice and the EO/LTTO solution three times, in each case with 1 week between applications. Only per-protocol outcomes were given, in which louse-free rates were 33 of 40 (82.5%) patients on day 21 for EO/LTTO, 13 from 36 (36.1%) on day 14 for the pyrethrin mousse, and 11 of 35 (29.7%) on day 14 for malathion shampoo. Application site adverse events were given for the ITT group as 18 events with EO/LTTO, three with the mousse, and two with the shampoo.

We found one RCT (91 children, 18 noncompliant) evaluating the effects of a shampoo product based on soya oil [70]. This study, conducted in the UK, compared two 30-min applications 9 days apart of soya oil shampoo with two 30-min applications of 0.5% permethrin alcoholic lotion. The soya oil shampoo was significantly ( $P < 0.01$ ) more effective than the lotion for both ITT and per-protocol populations. For the ITT analysis, 28/45 (62.2%) of the participants in the soya oil were louse free on day 14 versus 16/46 (34.8%) in the permethrin lotion group. The AD in rate of success was 27.4% (95% CI, 7–48%). For the per-protocol analysis the respective outcomes were 74.3% for soya oil versus 36.8% for permethrin, AD 37.5% (95% CI, 15–60%). Irritant adverse events were found in 12 people (26.6%) with the shampoo and 11 (23.9%) with the lotion.

**Drawbacks** No clinically detectable adverse effects have been reported for essential oils or herbal extracts, although a potential for toxic effects has been recognized for several essential oils, including anise [71]. One recent case report was of a grand mal seizure in a 4-year-old child triggered by use of a eucalyptus oil product used for treating head louse infestation [72]. It is likely that several essential oils or their components have similar activity to conventional insecticides, and would therefore be affected by similar resistance mechanisms. The tea tree oil component terpenin-

4-ol is recognized as an acetylcholine esterase inhibitor, similar to the activity of malathion, and is possibly affected by malathion resistance. Consequently, results obtained using one herbal combination are unlikely to translate to other herbal mixes using different active materials at different concentrations, especially where different terpenoids in a mixture could have antagonistic and inhibitory effects [73,74].

**Comment** Some activity against lice and their eggs has been identified in vitro, and in uncontrolled studies, for essential oils, their constituent terpenoids, and for several fixed oils (cold pressed), and other plant extracts [71,75–80]. Several products that have been released worldwide as medical devices or combing aids employ plant derived materials as “active” components. Many claim to be “clinically proven” but are not supported by published data from RCTs or even cohort studies.

Herbal and other alternative therapies have become more popular in this application, despite problems with efficacy or irritant side effects. Although terpenoids are a major constituent of some registered products, most alternative therapies use these chemicals at low concentrations to reduce the risk of side effects. Such low doses inevitably select for resistant strains of lice, and some resistance to terpenoids has already been observed in the UK (I.F. Burgess, unpublished).

## What is the best method for diagnosing louse infection?

### Case scenario 52.2

Head louse infections have been reported on some of the classmates of a 9-year-old girl. A few empty louse eggshells are visible on her hair, and she scratches occasionally. How can this evidence of what may be a past infection be distinguished from an active infestation? Is detection combing or direct observation (Figures 52.3 and 52.4) the most efficient way of finding lice?

### Efficacy

We found no systematic reviews and no RCTs evaluating detection methods. One observational study (224 people) compared traditional scalp inspection with wet combing with conditioner. Wet combing found more cases of louse infection in a school than scalp inspection: 49 of 224 (22%) versus 33 of 224 (15%), respectively. However, visual inspection was claimed to identify a further 13 cases not confirmed either by combing or by follow-up examination 2 weeks later [81]. One RCT of treatments found dry combing with a detection comb to be more effective than visual inspection in identifying positive cases before treatment: all of 25 (100%) versus 12 of 25 (48%) [5]. One observational study (268 children) compared the use of a metal louse detection comb with visual inspection of dry or slightly dampened hair [6]. Detection combing was found to be significantly more effective ( $P < 0.001$ ), identifying 68 of 268 (25.4%) children with lice in comparison with 16 of 268 (5.9%) for visual inspection. A second observational study (461 schoolchildren) used a plastic detection comb on dry hair [8]. Detection combing diagnosed lice on 96 of the 461 children (20.8%) in comparison with 30 (6.5%) in whom they were found by visual inspection [82]. In a third observational study (241 schoolchildren), two metal pin combs with different tooth spacing were each evaluated in a different school. A comb with 0.18 mm spacing found five children from 95 (5.3%) to have lice compared with a comb having a gap of 0.15 mm, which found five children infested out of 146 (3.4%). No infestations were detected by visual screening and



Figure 52.3 Standard detection comb for head lice.

there was no significant difference between the combs for efficiency of detecting lice or louse eggs [83].

#### **Comment**

Accurate diagnosis of an active head louse infestation is fundamental for deciding whether treatment is needed. The presence of apparently viable louse eggs close to the scalp was once considered sufficient evidence of an active infection. Now, only the presence of mobile stages is considered adequate evidence [10]. One cohort study (50 people) confirmed that the presence of eggs close to the scalp is a limited risk factor. Children screened by direct observation of the scalp, and found only to have louse eggs, were evaluated again 14 days later. Those with five eggs or more within 6 mm of the scalp were more likely to develop an active infestation than those with fewer than five eggs (seven of 22 vs two of 28). It was concluded that many children are excluded from school or treated unnecessarily and that repeated examinations to determine whether an infestation develops would be more beneficial [82].

Unnecessary treatments and school exclusions also arise because caregivers and health professionals misdiagnose items found in the hair. An observational study evaluating 614 samples of presumed head lice found that only 364 (59%) were louse related, showing that better diagnostic tools are required [84].

#### **Implications for practice**

Accurate diagnosis is essential for developing an appropriate treatment strategy. Treatment should only be given if living lice are found. Too often, children are exposed to treatments unnecessarily because a parent finds a few empty louse eggshells in the hair. However, if a child has never had head lice before, an infection may run for several weeks before it is discovered by chance, because there is no overt sign of the infestation [7,23]. Prescribers should therefore always ask for evidence of active infestation (e.g., a louse stuck to a piece of paper) before deciding on treatment.

#### **Can hair cutting or shaving be used to control head lice?**

There is a widespread belief that cutting hair short or even shaving of the scalp can either make it difficult for lice to live or may even



Figure 52.4 Detection combing for head lice using a standard plastic detection comb.

eliminate infestation, citing that boys suffer fewer infestations because they have shorter hair. The lower incidence and prevalence in boys is more likely associated with sociological factors and patterns of play rather than hair length [84,85]. Hair length per se is probably not a factor influencing infestation, but hair mass may be more important [86]. Certainly, greater masses of hair are more difficult to examine for presence of lice and may also present problems with respect to treatment application. In addition, grooming and styling practices probably have an influence on the survival of lice and their ability to establish a habitat [87–89].

Cutting hair short certainly makes grooming easier and finding whether lice are present much simpler. However, in itself it has no influence on either the presence or the survival of lice. Frequently, we have encountered boys with hair as short as 10 mm who have been virtually dismissed by parents as “never getting lice” who have actually had more parasites present than their longer haired girl siblings.

In some cultures it is commonplace for boys, and girls below a certain age, to have their heads shaved on a regular basis. This may be for control of parasites, for comfort during hot summer months, or in the belief that it makes the hair grow thicker or darker in color. Shaving was advocated by one writer as an effective and a safer practice than use of insecticides for eliminating lice, having experienced problems with poisoning when institutionalized retarded children licked each other's treated hair [90]. However, this practice was considered not to be acceptable in other cultural regions by a different correspondent on the basis that it is only a short-term solution, is stressful for children, and normally a last desperate measure for frustrated parents [91].

There is little or no evidence that hair shaving has any influence on the risk or persistence of infestation, and in order to ensure that it has any lasting effect shaving must be performed on a regular basis. In our clinical studies conducted in Bangladesh in the early

1980s we regularly encountered children who chose to shave their heads in hot weather. It was invariably the case that they were reinfested within a few days, when hair shafts were no longer than 2–3 mm, and we have also encountered an adult male in the UK who was infested despite having apparently shaved his head only 2–3 days previously (I.F. Burgess, unpublished data). Consequently, it can only be concluded that shaving and cutting of hair are of such limited effect that they should not be considered as part of a head louse control or elimination regimen.

### Key points

- Permethrin and malathion have limited efficacy against head lice, due to resistance. There is limited evidence for other insecticides such as lindane and phenothrin, which have now been withdrawn from most countries. Newer insecticides, such as spinosad and ivermectin, have only been evaluated versus placebo.
- Dimeticone is effective against head lice resistant to conventional insecticides and is a treatment of choice in many countries.
- Isopropyl myristate is also probably effective against head lice resistant to conventional insecticides.
- There is limited evidence for the effectiveness of oral cotrimoxazole, which is supposed to eliminate the symbiotic microorganisms associated with the gut of lice. Potential side effects associated with this material make it of limited applicability to head louse treatment.
- There is good evidence for oral ivermectin, although there are questions about dosing and long-term sustainability of what is probably a third-line treatment.
- There is insufficient evidence of the effectiveness of combing alone or in combination with insecticide treatment for either removing lice or nit combing.
- There is limited evidence for the effects of herbal treatments and essential oils as alternative treatments for head lice.
- Combing with a plastic detection comb appears to be the most effective method for finding live lice, but diagnostic methods have been little studied.
- There is no evidence of effectiveness for hair cutting or shaving.

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# Insect bites and stings

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## Background

### Definition

Insects comprise the most diverse group of animals on the Earth. The true insects are invertebrate species with six legs and three body segments: head, thorax, and abdomen. Many people would consider spiders, mites, and ticks as insects too, although these are arachnids, having eight legs and two body segments only. A more inclusive term than “insects” would be “arthropods,” comprising insects, arachnids, and other invertebrates with paired jointed legs [1].

Insect bites and stings are common occurrences. Bites often appear as wheals or extremely pruritic papules. Bee stings produce an immediate burning sensation and pain, followed by localized swelling and redness. Severe reactions such as anaphylactic shock can occur due to venomous stings [2]. Although these bites may seem inconsequential, insect-related diseases constitute a tremendous burden on the world's population.

This chapter focuses on common problems due to mosquito bites, Hymenoptera stings (bees, wasps), ticks, sand flies, and sand fleas.

### Incidence/prevalence

Insects are found in almost all parts of the world. Mosquitoes are considered the most common nuisance insects and the most important vectors of arthropod-borne diseases.

Blood-feeding insects carry and transmit various pathogens, leading to insect-borne diseases such as malaria and dengue. The World Health Organization estimates that there are 149–274 million cases of malaria yearly, resulting in 537 000–907 000 deaths in 2010 (WHO Global Malaria Programme 2011) [3]. The World Health Organization currently estimates there may be 50–100 million cases of dengue infection worldwide annually [4]. Systemic allergic reactions to insect stings have been reported to occur in 0.3–4% of individuals [5]. Deaths due to allergic reactions to Hymenoptera stings occur in 0.09–0.45 per million inhabitants [6].

Nuisance arthropod bites and the diseases they transmit have caused more loss to military troop strength than direct combat itself

[7]. About 70% of American army personnel reported experiencing significant problems because of arthropods, especially mosquitoes [8]. Work efficiency is also reduced by the nuisance of painful or pruritic bites, secondary infections, and allergies [7,9].

### Etiology/risk factors

Clinically important insects include mosquitoes, flies, lice, beetles, bedbugs, ants, bees, wasps, butterflies, moths, and fleas, among others [2].

Most venomous insects bite or sting in defense of their hives or nests. Nonvenomous insects bite in order to feed on human or animal blood. Biting insects such as mosquitoes and sandflies are generally considered a nuisance due to skin reactions to the bites. Substances in the insect's saliva cause allergic or irritant reactions. The bites are rarely harmful, but insects can be vectors of diseases, some of which are potentially fatal [2].

When bees sting, they leave the sting and venom sac attached. Venom continues to pump in through the stinger until the sack is empty or the sting is removed. Wasps and hornets, however, do not leave their stings behind and can sting repeatedly [10].

Many factors influence the feeding habits of arthropods, such as season, time of day, or preference for indoor or outdoor feeding [11]. Mosquitoes are attracted to human skin that is moist, warm, and with high levels of natural steroids on the skin surface. Persons who exhale more carbon dioxide (i.e., adults, pregnant women), certain odors, lactic acid, and types of sweat compounds also attract more mosquitoes [12].

### Aims of treatment

The aim of treatment is to reduce the severity and duration of local and systemic reactions to mosquito bites, Hymenoptera insect stings, and sand fleas (*Tunga penetrans*).

### Outcomes

- Risk reductions in the severity and duration of symptoms (itching, pain, swelling, local and systemic reactions such as urticaria, angioedema, hypotension, bronchospasm, anaphylactic shock).
- Adverse effects of treatment.

## Aims of prevention

- To reduce the risk of bites due to mosquitoes, ticks, sand fleas, and sand flies.

## Outcomes

- Number of insect bites or rates of insect catches.
- Protective efficacy or risk reductions of insect bites due to protective measure.

## Search methods

Search and appraisal (May 2012) of Medline (1966 to August 2012), Cochrane Library Issue 1, 2012, and the Cochrane Skin Group Specialized Register.

## Questions

### Case scenario 53.1

A 19-year-old man developed extremely pruritic, red papules on his arms and legs after an outdoor hike (Figure 53.1).

### How effective are treatments to reduce mosquito bite allergic reactions?

We found no systematic reviews.

#### Oral antihistamines versus placebo

We found two randomized, double-blind, placebo-controlled, crossover trials investigating oral antihistamines. Cetirizine 10 mg reduced immediate and delayed cutaneous reactions in 18 mosquito-sensitive patients who were exposed to mosquitoes in the field. After 24 h, the mean wheal size was reduced by 41% and the mean pruritus score was reduced by 67% [13].

A study investigated the efficacy of loratadine in 28 children (aged 2–11 years) who were sensitive to mosquito bites. Prophylactically administered loratadine (0.3 mg/kg) significantly decreased the mosquito bite wheal size by 45% and pruritus by 78% and also reduced the size of the bite lesions after 24 h [14].



Figure 53.1 Acute insect bite reactions on the leg.

### How effective is symptomatic treatment for skin reactions to mosquito bites?

We found no systematic reviews. There were no randomized controlled trials (RCTs) or controlled clinical trials investigating topical corticosteroids.

#### Topical treatments versus placebo

We found four RCTs that investigated topical remedies for mosquito bite lesions. A double-blind, placebo-controlled RCT conducted in 25 healthy individuals studied the effects of ammonium sulfate solution in relieving immediate cutaneous reactions to controlled mosquito bites. The ammonium solution reduced itching, burning, and pain and gave complete or partial relief in 64% of the treated forearms, in comparison with none in the placebo-treated arms [15].

Two RCTs studied homeopathic after-bite gels. A placebo-controlled, intraindividual RCT tested 68 healthy volunteers who were each bitten by laboratory-reared mosquitoes on three spots in the volar forearm. There were no statistical differences in pruritus and erythema between the treated, placebo, and untreated bite lesions [16]. A double-blind, intraindividual RCT tested a homeopathic after-bite gel (Prrrikweg gel) in 100 healthy volunteers and found no difference in erythema and pruritus in comparison with the placebo gel [17].

A double-blind RCT tested a topical antihistamine, dimethindene gel, with regard to relief of pruritus due to insect bites and sunburn. Mosquito bites were most frequently treated. If only the first bite or burn was taken into account, 88% were relieved by dimethindene ( $n = 49$ ) within 30 min of application, in comparison with 64% in the placebo group ( $n = 52$ ) ( $P < 0.01$ ) [18].

#### Drawbacks

Five patients (18.5%) reported mild sedation after 10 days of taking cetirizine, in comparison with two patients who took placebo after 5 days [10]. The children treated with loratadine had no marked side effects and tolerated the drug well [14].

No skin irritation or other side effects were reported after the application of topical ammonium or homeopathic gels. Both placebo and dimethindene gel had minor and transient side effects [15–18].

#### Comments

There are few RCTs on the treatment of a very common condition – mosquito bites and allergic reactions to these bites. The reduction of symptoms caused by insect bites has been evaluated for just two of the many oral antihistamines available and for only three types of topical treatment, which surprisingly did not include any topical corticosteroids. For such a common inflammatory skin disorder, insect bites and their treatment deserve further RCTs. The pruritus-relieving effects of dimethindene gel were not specifically for mosquito bites alone.

#### Implications for clinical practice

For mosquito bite-sensitive adults who anticipate exposure to mosquitoes, oral antihistamines such as 10 mg cetirizine may be taken prophylactically to reduce the allergic skin reactions. Loratadine may be given prophylactically to children with allergies to mosquito bites when exposure to these insects is highly possible.

For acute bites by mosquitoes, ammonium sulfate solution may be applied to alleviate the immediate burning, pain, and pruritus. Dimethindene gel may relieve pruritus due to insect bites. The after-

bite homeopathic gels tested have not shown significant benefit in persons without mosquito bite allergy. Topical corticosteroids have not been tested for efficacy in treating mosquito bites in controlled clinical trials or RCTs, but are commonly recommended for acute inflammatory skin reactions, including insect bites.

### What are effective personal protective measures against mosquito bites for travelers in campsites or wilderness locations?

There were no systematic reviews specifically on this topic, but one RCT was found on campers. Most of the evidence found was entomological studies among volunteers.

#### Electronic mosquito repellents

One Cochrane review found 10 field entomological studies that found no statistical difference between the number of mosquitoes caught on exposed body parts of participants using electronic mosquito repellents (EMRs) or no EMR. No quasi-randomized trials or RCTs were found on the efficacy of EMRs on malaria prevention. Marketing EMRs for mosquito bite or malaria prevention were not found to be justifiable [19].

#### Topical insect repellents

There were no systematic reviews or RCTs focusing on travelers. There was one systematic review of controlled laboratory experimental studies on citronella preparations in the prevention of mosquito bites. One broad narrative review that searched PubMed was found on plant-based repellents covering laboratory and field studies. One large field entomological study using a randomized, crossover design testing both plant-based and synthetic repellents was found. We found one RCT that tested a systemic, plant-based repellent against mosquitoes.

#### *N,N*-Diethyl-*m*-toluamide, icaradine, and para-methane-3,8-diol

One crossover RCT conducted in Senegal compared icaradine 20%, para-methane-3,8-diol 20% (PMD, from lemon eucalyptus), 50% *N,N*-diethyl-*m*-toluamide (DEET), and placebo used as spray lotions on the leg of 20 volunteers per day for 5 days. All four active products were statistically significantly superior to placebo and with no significant differences between the four active products

(Table 53.1). The protection afforded by DEET 50% tended to be superior to that of PMD 20% ( $P = 0.07$ ) [20].

#### Plant-based insect repellents

**Citronella repellent** One systematic review found 11 controlled laboratory and experimental published studies that investigated the efficacy of citronella oil or citronella with vanillin. Only one RCT was included. Protection time of citronella oil alone was at least 1.5 h against *Aedes* spp., 3 h against *Anopheles* spp., and 5 h against *Culex* spp. Citronella's protection time was significantly shorter than DEET's [21] (Table 53.2).

#### Systemic mosquito repellent: garlic capsules

One intraindividual, placebo-controlled, crossover RCT ( $n = 51$ ) investigated the mosquito repellence of ingested garlic capsules – two caplets the night before and two caplets at lunch on the day of the study. When volunteers were exposed to laboratory-reared *Aedes aegypti* mosquitoes, no significant mosquito repellence was noted [22] (Table 53.2).

#### Repellent-treated clothing and tents

**Repellent-treated patches** No RCTs were found focusing on travelers, but there was one field trial that tested pretreated patches worn as epaulettes over collars and as bands over cuffs and ankles of male military personnel in India. 12% *N,N*-diethyl-benzamide (Odomos)-, deltamethrin-, or cyfluthrin-impregnated patches, used alone or in combination, were tested on 30 male volunteers in a randomized, crossover trial. Combinations of deltamethrin or cyfluthrin with Odomos had greater repellency than any of the repellents used alone [23] (Table 53.3).

#### Permethrin-treated clothing combined with topical insect repellent use

One small RCT compared the protective effect of DEET 75% solution applied on exposed skin and permethrin-treated clothing, used alone or in combination. Eight male volunteers were exposed to natural populations of mosquitoes for 9-h daytime periods for 8 days. Unprotected test subjects were also exposed to mosquitoes to determine the overall biting rate. DEET combined with permethrin-treated clothing provided the best biting reduction (94.4%) in comparison with treated clothing alone (89.1%), although the difference

**Table 53.1** Topical insect repellents for mosquitoes.

Reference	Population	Species tested	Intervention	Comparison	Outcome	Results	Reporting quality/Comments
Uzzan <i>et al.</i> [20]	Senegal, western Africa $N = 100$ men and women (20 volunteers $\times$ 5 nights)	Various ( <i>Anopheles</i> , <i>Culex</i> , <i>Mansonia</i> , <i>Aedes</i> )	One application of repellent lotion sprays on one leg Crossover RCT • Icaradine 20% • PMD 20% (lemon eucalyptus) • DEET 50%	Placebo	Number of biting mosquitoes captured	Pooled data: 1868 mosquito captures • All four active products were statistically significantly superior to placebo • No significant differences between four active products • Protection afforded by DEET 50% tended to be superior to that of PMD 20% ( $P = 0.07$ ) • Similar protection among various species of mosquitoes • Protective effect of repellents were comparable at 8 p.m. and at midnight	Level 1 evidence Icaradine, PMD, and DEET repellent lotions were efficacious against various species of mosquitoes compared with placebo

Table 53.2 Plant-based repellents for mosquitoes

Reference	Population	Species	Study design/ intervention	Comparison	Outcomes	Main results	Study quality/ Comments
Kongkaew <i>et al.</i> [21]	Human subjects	<i>Aedes</i> <i>Anopheles</i> <i>Culex</i>	Systematic review of controlled clinical trials or RCTs Entomological studies: room or cage method Citronella oil or citronella with vanillin	DEET or negative control (placebo or untreated skin)	Protection time or percentage repellency	<i>N</i> = 11 clinical trials (one RCT only) <i>N</i> = 6 studies: mean protection time (SD) of citronella alone [86.28 min (56.22)] was shorter than that in the DEET group [342.73 min (99.27)] Protection time of citronella oil alone is at least 1.5 h against <i>Aedes</i> spp., 3 h against <i>Anopheles</i> spp., and 5 h against <i>Culex</i> spp.	Level 2 evidence (SR of 10 controlled clinical trials, one RCT) Citronella oil used in a variety of preparations is less effective than DEET in terms of duration of protection against mosquitoes Citronella oil could provide sufficient protection time against mosquitoes
Rajan <i>et al.</i> [22]	49 adult volunteers	<i>Aedes aegypti</i> (laboratory reared)	Crossover study (intra-individual RCT); wash-out 28 days Ingestion of two caplets of garlic (a caplet equal to one clove of garlic) (one visit)	Placebo (lactose)	<ul style="list-style-type: none"> <li>No. of visible mosquito bites</li> <li>Weights of mosquitoes after feeding</li> <li>Amount of blood ingested (weights of mosquitoes)</li> <li>Amount of human serum albumin (HSA) within mosquitoes</li> </ul>	<ul style="list-style-type: none"> <li>No significant differences between groups</li> <li>Lower HSA content in placebo group</li> </ul>	Level 1 evidence Ingestion of two caplets of garlic did not have significant repellence compared with placebo Limitation: 1 day ingestion of garlic only

Table 53.3 Repellent-treated clothing and tents for mosquito bites.

Reference	Population	Species tested	Intervention	Comparison	Outcomes	Results	Reporting quality/ Comments
Bhatnagar and Mheta [23]	Male military personnel in a garrison, northeast India <i>N</i> = 30 per group × 5 groups (crossed over to each treatment group)	Not specified	Pretreated patches: epaulettes over collars, bands, over cuffs and ankles 1 Deltamethrin 2 Cyfluthrin 3 Deltamethrin+Odomos 4 Cyfluthrin+Odomos	12% <i>N,N</i> -diethyl-benzamide (Odomos)-impregnated patches	Per man-hour biting rate Per man-hour mosquito catches	Deltamethrin or cyfluthrin alone had comparable repellencies compared with Odomos alone Deltamethrin and cyfluthrin had comparable repellencies	Level 1 evidence Large sample size for an entomological study Combinations of deltamethrin or cyfluthrin with Odomos had greater repellency than any of the repellents used alone
Schreck <i>et al.</i> [24]	Eight test subjects	<i>Aedes taeniorhynchus</i> (Wiedemann)	DEET on skin With or without permethrin on clothing 9 h daytime × 8 days/treatment	No DEET on skin With or without permethrin treated clothing 9 h daytime × 8 days/treatment	Number of bites Per 9-h days	DEET + permethrin-treated clothing = 1.5 bites Permethrin-treated clothing only = 53.5 bites DEET only = 98.5 bites Untreated clothing only = 2287 bites (extrapolated) Permethrin-treated clothing reduced biting rates within immediate area by 90%	Level 2 evidence (small sample size) Permethrin-treated clothing combined with DEET on exposed skin afforded a very high protective efficacy against mosquito bites
Boulivaire and Beisang [25]	North America Boy Scout Camp <i>N</i> = 545 (80% boys, 20% adults) From 8 camp sites Treatment group = 761 person-nights Control group = 853 person-nights	Not stated	0.4% permethrin (2.5% permethrin diluted by 7 parts water) sprayed onto external surface of canvass tents Topical insect repellent permitted	No permethrin sprayed onto tents Topical insect repellents permitted	No. of mosquito bites and landings per 5 min	Total 1614 person-nights Average bites per 5 min = 5.1 ± 7.2 (SD) permethrin-treated tents as control RRR mosquito bites and landings = 44% (95% CI: 34–55%) <i>p</i> < 0.001 Insect repellents as control RRR = 36% (95% CI: 25–47%) <i>p</i> < 0.001 – used only during 32% of nights Permethrin vs insect repellent RRR = 20% (95% CI: 4–37%) <i>p</i> = 0.01	Level 1 evidence Pragmatic study design Permethrin-treated tents provided effective passive prophylaxis against mosquito bites



was not significant. There was also no significant difference in bite reduction between DEET (68.7%) and unprotected controls (65.9%), due to bites through untreated clothing [24] (Table 53.3).

**Permethrin-treated tents** One double-blind RCT was conducted among North American campers ( $n = 545$ ), with campsites being randomly allocated to have permethrin-treated tents or untreated tents. The external surface of canvas tents were sprayed once with 0.4% permethrin. The campers were reminded, by means of hand-outs and posted signs, to apply DEET insect repellent within 2 h of dusk. Through daily surveys, mosquito landings and bites (for 5 min at dusk) as well as insect repellent use were self-reported by campers. Permethrin treatment of tents significantly reduced the number of mosquito bites at dusk among campers by 44% (relative risk reduction [RRR]; 95% confidence interval [CI], 33.8–54.7%;  $P < 0.001$ ). Insect repellent use reduced mosquito landings and bites by 36% (95% CI, 25–47%;  $P < 0.001$ ), but no additional benefit was observed among campsites that had permethrin-treated tents. Insect repellent usage only occurred consistently in 15% of subjects [25] (Table 53.3).

### Drawbacks

**Electronic mosquito repellents** Despite the insufficient evidence regarding their efficacy, electronic mosquito repellents are widely marketed and may give a false sense of protection to consumers.

**Topical insect repellents** DEET can dissolve plastic and vinyl and damage rayon, spandex, pigmented leather, and acetate. DEET has reportedly caused dermatitis, allergic reactions, and cardiovascular and neurologic toxicities [12].

Two large case series from poison control centers indicate that the risk of DEET is low. In a 5-year retrospective study conducted in the 1980s, there were five major adverse reactions reported after 9086 exposures to DEET (0.05%). These included hypotension, hypotonic reaction, and syncope, and one death (a suicide ingestion) [26].

In the second report, major adverse reactions to DEET use occurred in 0.1%. These included hypotension, seizures, respiratory distress, and two deaths (0.01%). Among infants and children only, there were 10 major events among 17 252 reported exposures (0.06%), and no deaths. Infants and children accounted for 83.1% of all reported exposures, but the majority of the serious outcomes occurred in adults [27].

**Plant-based insect repellents** Plant-based repellents may contain hazardous ingredients [28], and ingestion of essential oils such as citronella can lead to poisoning [29]. No adverse events were reported after garlic ingestion.

**Repellent-treated clothing or fabric** There were no reported adverse events associated with cloth patches treated with synthetic pyrethroids such as 12% *N,N*-diethyl-benzamide (Odomos), deltamethrin, or cyfluthrin. Although relatively safe and long-lasting when applied to clothing or fabric, permethrin is not recommended as a topical repellent because of safety concerns (e.g., neurotoxicity) upon chronic exposure [30,31].

### Comments

***N,N*-Diethyl-*m*-toluamide insect repellent** The RCTs found had small sample sizes and did not have allocation concealment or blinding. RCTs with adequate sample sizes and improved method-

ology will be able to provide better estimates of the effectiveness and safety of DEET in comparison with no protection or other measures.

**Plant-based insect repellents and alternatives to *N,N*-diethyl-*m*-toluamide** The systematic review on oil of citronella was mainly based on nonrandomized, controlled clinical trials and has a risk of bias. The RCT that investigated garlic may not have detected any effect because only a small dose was ingested. Further clinical trials with increased doses of garlic may be pursued.

There are few RCTs on insect repellents against mosquitoes, but many controlled clinical trials that use DEET as the “gold standard” for testing other chemical and botanical preparations (e.g., IR3535, picaridin, oil of eucalyptus, soy oil, and citronella). RCTs are needed to further validate the effectiveness and safety of these repellents, because some of these are already commercially available, while others may be developed for commercial use and may benefit the countries that possess these indigenous herbs.

**Repellent-treated clothing and tents** The 5-min counts of mosquito bites and landings were reported by campers themselves, creating variability in the outcome measurement. The large sample size and the “real-world” setting of the trial may have offset this limitation of self-reporting. This RCT did not primarily study the effects of insect repellents or DEET in particular, therefore creating bias in the reported estimate of its efficacy.

### Implications for clinical practice

Travelers to mosquito-endemic areas can achieve high levels of sustained protection against bites by using permethrin-treated clothing as well as treated tents. In addition, insect repellents such as DEET may be applied on exposed skin.

Permethrin, like its derivatives, has the advantage of being an insect repellent and an insecticide as well. It is poorly absorbed through the skin and remains active in fabrics even after laundering. It is also quite effective against ticks. DEET has been used worldwide for over 40 years and is found in many commercial insect repellents. It has the added advantage of repelling black flies, chiggers, fleas, and midges as well [12].

The RCTs identified provide evidence regarding efficacy, but do not delve into the practical use of protective measures. The following are suggestions for use based on non-RCT studies and guidelines.

- Avoidance of the insects' habitats, barrier protection (e.g., clothing, bednets), and insect repellents are general measures to prevent insect bites [32]. The combination of “avoid, cover up, and repel” is recommended.
- Mosquitoes can be avoided by staying indoors in insect-proofed dwellings when mosquitoes actively bite – often from dusk to dawn. When outdoors, clothes covering most body parts would be ideal, and the addition of permethrin or other repellents on the fabric would provide a high degree of protection.
- Users must also be reminded that insect repellents do not repel all insects at all times. The repellents must be applied to all exposed areas of skin, because unprotected skin a few centimeters away from a treated area can be attacked by hungry mosquitoes [33].
- The following factors may affect the effectiveness of the repellent: the frequency and uniformity of application, the number and species of the insects, the user's inherent attractiveness to

blood-sucking arthropods, and the overall activity level of the exposed individual [34]. Topical repellents' effectiveness may be reduced when rubbed off or removed by contact with clothing, evaporation and absorption from the skin surface, wash-off from sweat or rain, higher temperatures, or a windy environment [33,35].

- On the basis of a controlled clinical trial, increasing the concentration of DEET does not improve protection but does provide a longer duration of protection. Concentrations of 6.65% protect for about 2h, while 23.8% DEET can last about 5h [36]. The concentrations available for DEET range from 5% to 100%, although the latter is rarely used or indicated. Reapplications are necessary, especially in hot, humid weather, because DEET loses 50% of its effectiveness with every 10° rise in temperature [36].
- Practice guidelines often recommend only one application of low-dose DEET in children, even though the repellent may provide protection for only a few hours. Since there is a lack of evidence on the toxicity of low-dose DEET, reapplication may be done if the child is outdoors for about 4h or more, and especially after swimming or bathing [37].
- The likelihood of side effects would be minimized if the lowest effective concentration of DEET were used for a given situation. Insect repellents and insecticides may have toxic effects, but with proper adherence to the Environmental Protection Agency guidelines and advisories by disease control agencies, these protective measures can be a safe means of preventing insect bites and vector-borne diseases.

### Are insect repellents safe for use among pregnant women? Safety

One vehicle-controlled RCT was conducted in a refugee camp among pregnant women in their second and third trimester of pregnancy (Table 53.4). For an average of 18 weeks, women applied 1.7g DEET per day with thanaka, a paste derived from *Limonea acidiosima* and used as a carrier of the DEET repellent ( $n = 449$ ). The control group applied thanaka 3.2g/day ( $n = 448$ ).

The median total DEET dose was 214.2g per woman (range 0–345.1g). There were no adverse effects on survival, growth, or development at birth or at 1 year among the patients' infants. DEET was detected in 8% of 50 cord blood samples from babies of randomly selected mothers. DEET was not detected in urine samples, indicating efficient clearing of the chemical from their systems. DEET usage reduced the risk of scabies (risk ratio [RR], 0.70; 95% CI, 0.5–0.97), but not of fungal infections. There were no significant adverse neurologic or gastrointestinal effects on the women [38].

### Drawbacks

Skin warming was more frequent among DEET users than thanaka users (80% vs 57.6%;  $P < 0.001$ ). DEET absorption may be enhanced by breaks in the skin; for example, in the presence of other skin diseases. Liver or kidney impairment may also lead to toxicity.

### Comments

In the same cohort of pregnant women, the RCT also investigated the protective effects of DEET against malaria. The RRR was 28% for falciparum malaria and 9% for vivax malaria. However, these results were not statistically significant [39].

### Implications for clinical practice

Evidence from the single RCT including 897 pregnant women suggests that DEET in 20% solution form is safe for pregnant women in their second and third trimesters and does not result in adverse effects on their infants. There has been no evidence so far that DEET is a health risk to pregnant and lactating women or their infants. Potential toxicity exists in conditions that enhance DEET percutaneous absorption or impair its clearing from the body.

### Case scenario 53.2

A 40-year-old man complained of pain and swelling on his hand after being stung by a bee. He was also experiencing difficulty in breathing.

### What symptomatic treatment is effective for skin lesions due to bee or wasp stings?

No systematic reviews were found on this topic. Two RCTs evaluated symptomatic treatment of local reactions after stings by bees, wasps, or hornets (Hymenoptera).

### Pinching versus scraping off the bee sting left in the skin

We found one RCT with two volunteers who either pinched or scraped off honeybee stings (20 stings in each group). The wheal response was greater for stings removed by pinching than for those removed by scraping (80 mm<sup>2</sup> vs 74 mm<sup>2</sup>), but the difference was not statistically significant [40].

### Topical aspirin paste versus ice pack

One RCT studied patients who had just been stung by bees or wasps and who had called a poisons information center for advice. The aspirin group (37 patients) were instructed over the telephone to apply an ice pack followed by topical aspirin paste. The patient was

**Table 53.4** Safety of insect repellents during pregnancy.

Ref.	Population	Species tested	Intervention	Comparisons	Outcomes	Results	Study quality/Comments
McGready <i>et al.</i> [38]	Thai–Burmese border camp $N = 897$ Pregnant women on 2nd and 3rd trimester DEET group = 449 Thanaka = 448 $N = 50$ cord blood samples Randomly selected		$N = 449$ 1.7g DEET per day application with or without thanaka – applied daily after evening shower on exposed arms and legs	$N = 448$ Thanaka 3.2g/day = paste derived from <i>Limonea acidiosima</i> used as carrier of the repellent	Adverse effects on fetus at birth and at 1 year Adverse effect on women	214.2g total median dose DEET/pregnancy $\times$ 18 weeks (average) No adverse neurologic, gastrointestinal, or dermatologic effects on women Median total dose = 214.2g DEET (range 0–345.1g) No adverse effects on survival, growth, or development at birth or at 1 year DEET detected in 8% of cord blood samples	Level 1 evidence Large sample size Pragmatic study design Pregnant women applying DEET lotion daily, with or without thanaka, was not harmful for the fetus at birth and at 1 year

instructed to add a few drops of water to a soluble aspirin tablet and spread this paste over the affected skin. The control group (19 patients) was instructed to apply an ice pack alone to the stings. Swelling at 12 h had resolved in 57% of the aspirin group and in 74% of the ice-pack group (absolute risk reduction,  $-14\%$ ; 95% CI,  $-39\%$  to  $-14\%$ ). Pain at 12 h had resolved in 81% of the aspirin group and 95% of the ice-pack group. Redness persisted for a median duration of 6 h in the aspirin group and only 2 h in the ice-pack group. In both the intention-to-treat and per-protocol analyses, topical aspirin paste was not significantly better than ice packs in reducing pain, swelling, and pruritus [41].

#### **Topical corticosteroids**

No RCTs or controlled clinical trials were found.

#### **Drawbacks**

Topical aspirin paste reportedly increased the duration of redness at the sting sites in comparison with ice-pack application.

#### **Comments**

The RCT on methods of removing stingers also determined that the stinger of honeybees should be immediately removed by whatever means possible, because the time during which the stinger remains embedded in the skin determines the degree of envenomization.

The RCT on topical aspirin assessed clinical effects through telephone interviews, not actual physical examination of patients, although care was taken to standardize the quantification of symptoms.

There are very few RCTs on topical or symptomatic treatments for localized reactions to bee or wasp stings, despite the frequency of this condition. Corticosteroids and antihistamines are often mentioned in treatment guidelines, but there are no RCTs focusing on this topic.

#### **Implications for clinical practice**

Honeybee stings should be removed immediately either by pinching, scraping, or other means in order to reduce the degree of envenomization. Ice packs or aspirin paste may reduce local swelling, pain, and pruritus, but aspirin may prolong redness due to its inherent irritant properties.

#### **What symptomatic treatment is effective for systemic reactions to accidental bee or wasp stings?**

We did not find any systematic reviews or RCTs focusing on this topic.

#### **Implications for clinical practice**

Despite the absence of systematic and reliable evidence in the specific context of insect stings, it is important to know that anaphylactic reactions to insect venoms can be treated in the same way as anaphylaxis from any other cause. Sympathomimetics, antihistamines, and corticosteroids are the most effective drugs for dealing with systemic allergic reactions [42]. For severe reactions (e.g., respiratory or cardiovascular symptoms), two RCTs showed that intramuscular epinephrine was superior to subcutaneous injections in terms of the rapid increase in plasma concentration and start of pharmacological effects [43,44].

An emergency kit for self-medication has been recommended for patients with a known history of systemic reactions. One RCT reported that children (15–30 kg) who self-injected premeasured epinephrine (EpiPen 0.30 mg) had more adverse effects than those

using a lower dose preparation (EpiPen Jr 0.15 mg) [45]. One RCT studied the efficacy of subcutaneous versus inhaled epinephrine preparations among healthy individuals and reported that absorption of epinephrine was more rapid with the inhaled epinephrine [46]. Another RCT reported that 19 children with histories of anaphylaxis were unable to inhale sufficient epinephrine, due to the numerous inhalations required and the bad taste [47].

#### **Is venom immunotherapy effective in preventing systemic reactions to Hymenoptera stings?**

We found one Cochrane systematic review that assessed the efficacy and safety of extracted insect venom on the prevention of further allergic reactions to insect stings [48]. Six RCTs and one quasi-randomized trial of venom immunotherapy (VIT) using standardized venom extract were included with a total of 392 participants. This review covered ant, wasp, and bee immunotherapy. Sublingual (one trial) and subcutaneous VIT (six trials) were tested on individuals with either large local sting reactions or systemic reactions.

This review found that VIT was effective for preventing systemic allergic reactions to insect stings (RR, 0.10; 95% CI, 0.03–0.28). VIT was effective for preventing large local reactions to insect stings (five studies; 112 follow-up stings; RR, 0.41; 95% CI, 0.24–0.69) and for improving quality of life (mean difference (MD) in favor of VIT 1.21 points on a seven-point scale; 95% CI, 0.75–1.67).

#### **Drawbacks**

The Cochrane review on VIT found a small but significant risk of systemic adverse reactions to VIT (RR, 8.16; 95% CI, 1.53–43.46; two studies contributed to the effect estimate). The authors analyzed 11 observational studies and reported that 131/921 (14.2%) participants treated with bee venom VIT and 8/289 (2.8%) treated with wasp venom VIT experienced systemic adverse reactions.

A prospective multicenter study reported that 20% of 840 patients developed systemic reactions to VIT. Systemic reactions occurred in 1.9% of injections during the dose-increase phase and 0.5% of injections during the maintenance phase. The majority of the reactions were mild. Risk factors for systemic reactions were bee venom extract, female gender, and rapid dose increase (rush regimen), but not the severity of insect sting reactions [49].

#### **Comments**

Hymenoptera venom hypersensitivity is potentially life threatening, thus making double-blind, placebo-controlled trials appear unethical. This may explain why only a few RCTs were found. The systematic review on VIT presents good evidence of its efficacy and safety, although some risk of bias was present due to the lack of allocation concealment in five of the trials.

#### **Implications for clinical practice**

VIT, whether sublingual or subcutaneous, showed protective benefit in all studies in terms of reducing the risk of immediate and long-term bee or wasp sting reactions and improving quality of life. Benefit was noted especially for those with prior severe systemic reactions to Hymenoptera venom. In nearly all studies, the effect of VIT was evaluated by measuring the recurrence rates of systemic reactions to re-stings in patients with previous systemic events. Patients with a known history of systemic reactions must be aware that they are at risk of potentially life-threatening reactions to re-stings.

### Does pretreatment with antihistamines reduce the risk of adverse effects of venom immunotherapy?

We found no systematic reviews. Four RCTs have compared oral antihistamines with placebo in rapid dose-increase VIT regimens.

In 140 patients, cetirizine significantly reduced local adverse reactions, but not systemic adverse reactions [50]. In 54 patients, fexofenadine 180 mg given on days 1, 8, 22, and 50 significantly reduced local adverse reactions, but not systemic adverse reactions [51].

In one RCT ( $n = 52$ ), terfenadine 120 mg twice daily significantly reduced local adverse reactions, but not respiratory or cardiovascular symptoms [52].

In the second RCT ( $n = 121$ ), pretreatment with 120 mg terfenadine or terfenadine plus ranitidine significantly reduced both systemic adverse reactions and local adverse reactions during the first week of rush immunotherapy. Therapeutic benefit was evident during the first 4 weeks of treatment [53].

### Drawbacks

Side effects of the antihistamine pretreatment were reported in only one of the above RCTs: headache in 2% (two of 82) and nausea in 1% (one of 82) of the patients who received terfenadine, and fatigue in 3% (one of 39) of those who received placebo.

### Comment

The influence of premedication with terfenadine was assessed after an average of 3 years' follow-up. None of the 20 patients who received terfenadine prior to VIT had reacted to subsequent bee-sting challenges, whereas six of 21 (29%) of the placebo pretreatment group had mild to moderate systemic allergic reactions. These findings indicate that the efficacy of VIT was not adversely affected and may have been enhanced by antihistamine premedication [54].

### Implications for clinical practice

The data suggest that pretreatment with antihistamines such as cetirizine, fexofenadine, and terfenadine may reduce cutaneous adverse reactions to rush or ultra-rush VIT. Terfenadine with or without ranitidine may reduce systemic adverse reactions during the first 4 weeks of rush VIT. The efficacy of VIT is not affected by antihistamine premedication.

### Case scenario 53.3

A 30-year-old male hikes through the woods and notices several ticks attached to his clothing and exposed skin, causing an itchy rash.

### What protective measures are effective against tick bites?

Two RCTs investigating topical repellents, one RCT on color of clothing, and two RCTs on education intervention packages were found (Table 53.5).

### Topical repellents

Two RCTs were found on topical repellents for the prevention of tick bites. DEET plus ethylbutylacetylaminopropionate (EBAAP) was applied daily by forestry workers on exposed skin and compared with placebo ( $N = 276$ ). Total repellent effectiveness (TRE) against tick attachment was reported as  $RRR = 41.1\%$  (95% CI, 2.5–79.6%) and TRE on arms was 66% (95% CI, 17.3–114.7%). Combination of DEET and EBAAP topical repellent on exposed skin was considered moderately effective in reducing the risk of tick bites compared with placebo [55].

Lemon eucalyptus extract (citriodiol) spray was applied daily by healthy volunteers for 2 weeks to lower extremities then crossed over to no repellent use for another 2 weeks ( $N = 111$ ). The median number of attached ticks per person decreased from 1.5 (range 0–9) to 0.5 (range 0–2) ( $P < 0.05$ ) during citriodiol use [56].

### Dark versus light clothing

Ten healthy volunteers wore light-colored clothing and were crossed over to dark clothing on different days before they walked through a tick-infested area. A mean difference of 20.8 more ticks per person were found when light-colored clothing was worn [57].

### Educational programs

One RCT evaluated the effectiveness of a theory-based educational program to prevent Lyme disease and other tick-borne illnesses (TBIs). Among 30 164 ferry passengers traveling to an endemic area, there were lower rates of TBI among participants receiving TBI education compared with control participants receiving bicycle safety education (RR, 0.79). A 60% reduction in risk was observed among those receiving TBI education among those who visited the endemic area for more than 2 weeks compared with control participants (RR, 0.41; 95% CI, 0.18–0.95;  $P < 0.038$ ). Precautions (i.e., use repellent, protective clothing, limit time in tick areas) and checking themselves for ticks were also significantly more likely among TBI-educated participants [58].

Another RCT compared the effects of tick-related educational material versus general health-related educational material, both delivered bimonthly through mail to 317 residents of an endemic area for Lyme disease. After the 6-month intervention period, tick-related educational material was associated with an increase in the knowledge, attitude, behavior (KAB) measures in the intervention group, but this change was not associated with change in anti-recombinant tick calreticulin antibody (ARTCA) levels [59].

### Drawbacks

There were no reported adverse effects associated with EBAAP and citriodiol topical repellents or the education packages tested.

### Comments

The RCTs testing topical repellents, clothing, and education interventions used pragmatic study designs and large sample sizes, thus increasing the strength of evidence regarding their effectiveness.

### Implications for clinical practice

Topical repellents containing a combination of DEET and EBAAP (also known as IR3535) or lemon eucalyptus extract (citriodiol or PMD) may provide moderate protection against tick attachment and should be applied on exposed skin by travelers or workers in tick-infested areas. Education packages are effective in the prevention of TBIs and should be implemented in areas that are endemic for Lyme disease and other TBIs.

### Case scenario 53.4

A 9-year-old boy from an urban squatter settlement in Brazil has intense pruritus, inflammation, and pain on his heels and toes due to sand fleas (*Tunga penetrans*).

### What are effective treatments and preventive measures for sand flea infestations?

One RCT on prevention and two RCTs on treatment were found, all conducted in Brazil (Table 53.6).



Table 53.5 Preventive measures for tick bites.

Ref.	Population	Species tested	Intervention	Comparison	Outcome/s	Main Results	Comments
Staub <i>et al.</i> [55]	Switzerland N = 276 Forestry workers and orienteers N = 138 per group	NS	Combination DEET and EBAAP topical repellent on exposed skin ×6 months	Placebo ×6 months	RRR or percentage effectiveness Average no. of ticks per hour spent in wooded areas	(1) Average number of ticks per hour spent in wooded areas: Repellent = 0.17 placebo = 0.10 $p < 0.05$ (2) Total repellent effectiveness (TRE) against tick attachment: RRR = 41.1% (95% CI, 2.5–79.6%) TRE on arms = 66% (95% CI, 17.3–114.7%) No significant difference in average of unattached ticks	Level 1 evidence Combination DEET and EBAAP topical repellent on exposed skin is moderately effective in reducing the risk of tick bites compared with placebo
Gardulf <i>et al.</i> [56]	Sweden N = 111 volunteer healthy, outdoor active adults living in highly infested areas	<i>Ixodes ricinus</i>	Lemon eucalyptus extract (citriodiol) spray daily ×2 weeks to lower extremities then crossover to no repellent use	No repellent on any part of body for 2 weeks then crossover to lemon eucalyptus spray ×2 weeks	Number of observed attached ticks, not yet attached ticks Anatomical location of ticks	Citriodiol group = 42 attached ticks during use No citriodiol = 112 attached Median number attached ticks per person decreased from 1.5 (range 0–9) to 0.5 (range 0–2) $P < 0.05$ during citriodiol use Number of attached ticks below waist: 13/42 (31%) with citriodiol 73/112 (65%) without spray $p < 0.001$	Level 1 evidence Lemon eucalyptus extract spray (citriodiol) on lower extremities is effective in reducing the number of attached ticks compared with no repellent use Limitation: total tick count used
Stjernberg and Berglund [57]	Sweden 10 volunteers	NS	Light clothing (alternately worn before new exposure)	Dark clothing (alternately worn before new exposure)	No. of bites on clothes No. of nymphs, adult ticks	886 nymph ticks collected overall mean differed significantly 20.8 more ticks per person on light clothing All participants with light clothing had more ticks in all periods of exposure	Level 2 evidence Small sample size Dark clothing may reduce the number of ticks compared with light-colored clothing
Daltroy <i>et al.</i> [58]	Travelers to southeastern Massachusetts, USA N = 30 164 ferry passengers	NS	Theory-based educational program on prevention of Lyme disease and tick-borne illnesses (TBIs)	Bicycle safety education	Precautionary and tick check behaviors	<ul style="list-style-type: none"> <li>Lower rates of TBI among participants receiving TBI education compared with control participants receiving bicycle safety education (relative risk, RR = 0.79)</li> <li>60% reduction in risk among those receiving TBI education who visited the endemic area for more than 2 weeks compared with control participants (RR = 0.41, 95% CI, 0.18–0.95, <math>p &lt; 0.038</math>)</li> <li>Precautions (i.e., use repellent, protective clothing, limit time in tick areas) and checking themselves for ticks were also significantly more likely among TBI-educated participants</li> </ul>	Level 1 evidence Theory-based Lyme disease prevention program can increase precautionary behavior and result in a significant reduction in TBI
Malouin <i>et al.</i> [59]	Baltimore, MD, USA N = 317 Endemic area for Lyme disease	NS	Tick-related educational material Bimonthly through mail ×6 months	General health-related educational material Bimonthly through mail ×6 months	(1) Knowledge, attitude, behavior (KAB) response through questionnaire (2) Anti-recombinant tick calritectulin antibody (ARTCA)	(1) Tick-related education material – increased percentage desired response on KAB measure related to examining body for tick and insect repellent use (2) Only 6/37 models had significant relation between change in KAB and change in ARTCA levels	Level 1 evidence Tick-related educational material was associated with an increase in the KAB measures in the intervention group, but this change was not associated with change in ARTCA levels

### Topical plant-based repellent lotion: coconut oil, jojoba oil, Aloe vera lotion (Zanzarin)

The sand flea infestation of 131 children and adults was first treated with coconut oil, jojoba oil, *Aloe vera* lotion (Zanzarin) for 4 weeks before they were randomly assigned to one of three cohorts: twice-daily application for 1 week every second week or every fourth week or no application of any repellent over a 5-month period after initial

treatment. The intensity of infestation, viable lesions, proportion of manipulated lesions, and clinical pathology were all reduced significantly, especially when Zanzarin was applied every 2 weeks [60].

### Ivermectin, metrifonate, thiabendazole lotions and ointment

In an earlier study, ivermectin, thiabendazole, metrifonate lotions, and thiabendazole ointment were tested on 108 children and adults

Table 53.6 Prevention and treatment of sand fleas infestation.

Ref.	Population	Species tested	Intervention	Comparison	Outcomes	Main results	Study quality/Comments
Buckendahl et al. [60]	Brazil N = 131 Cohort 1: 46 Cohort 2: 34 Control: 51	<i>Tunga penetrans</i>	Coconut oil, jojoba oil, <i>Aloe vera</i> lotion (Zanzarin) Phase 1: twice daily application on feet $\times$ 4 weeks Phase 2: 5 months Cohort A: apply twice daily every 2nd week Cohort B: apply twice daily every 4th week	Cohort C: no application	<ul style="list-style-type: none"> <li>Intensity of infestation</li> <li>Viable lesions</li> <li>Percentage manipulated lesions</li> <li>Clinical pathology</li> </ul>	Cohort 1 (intermittent application of Zanzarin for 1 week every 2nd week) significantly reduced infestation intensity from a median 4 lesions (IQR 1–9) during the whole transmission season Cohort B (application of the repellent every 4th week): infestation intensity remained twice as high (median 8 lesions, IQR 9–16; $p = 0.0035$ ) Control cohort C: infestation intensity 3.5 times as high (median 14 lesions; IQR 7–26; $p = 0.004$ ) Tungiasis-related acute pathology very low in cohort A (median severity score 2; IQR 1–4) compared with cohort B (median severity score 5; IQR 3–7; $p = 0.001$ ), and control cohort C (median severity score 6.5; IQR 4–8; $p = 0.001$ )	Level 1 evidence Moderate risk of bias – blinding of patients, clinicians, and outcome assessors not possible due to distinctive odor of lotion Reinfestation and tungiasis-associated morbidities can be minimized through intermittent application of a plant-based repellent lotion (coconut oil, jojoba oil, <i>Aloe vera</i> )
Heukelbach et al. [61]	Brazil Children >1 year old and adults N = 108 No. of feet infested: 169	<i>Tunga penetrans</i>	Ivermectin lotion Thiabendazole lotion Thiabendazole ointment Metrifonate lotion	Placebo lotion	No. of lesions on feet	Ivermectin lotion, metrifonate, thiabendazole ointment and lotion can each significantly reduce the number of lesions	Level 1 evidence
Heukelbach et al. [62]	Brazil Children >5 years old and adults Total N = 54 Ivermectin: 27 Placebo: 27 Total no. lesions: 192	<i>Tunga penetrans</i>	Ivermectin (oral) 300 $\mu$ g/kg body weight Single dose Repeated after 24 h	Placebo	<ul style="list-style-type: none"> <li>Clinical stage of lesion</li> <li>Presence of erythema pain, itching, signs of viability of fleas</li> <li>Total lysis of fleas</li> </ul>	<ul style="list-style-type: none"> <li>Ratio of total lysis per total number of fleas was slightly higher in ivermectin group</li> <li>No significant difference on any other outcome measures</li> </ul>	Level I evidence Low risk of bias Oral ivermectin 300 $\mu$ g/kg body weight given at 2 doses 24 h apart was not proven to be efficacious for treatment of embedded sand fleas

and found to significantly reduce the number of lesions on their feet compared with placebo lotion [61].

### Oral ivermectin

Oral ivermectin was given at 300  $\mu$ g/kg body weight single dose and repeated after 24 h to 54 patients who were over 5 years of age. The ratio of total lysis per total number of fleas was slightly higher in the ivermectin group and no significant difference on any other outcome measures was observed when compared with placebo [62].

### Drawbacks

There were no adverse events reported among patients who used the topical repellents. For oral ivermectin, adverse events were reported in six cases. Three patients complained of headache, two of abdominal pain, and one of sore throat. In the placebo group, three patients complained of headache and three of pruritus.

### Comments

The study on Zanzarin repellent had a moderate risk of bias because blinding of patients, clinicians, and outcome assessors was not possible due to the distinctive odor of the lotion. Nevertheless, this RCT showed good evidence of its preventive efficacy against tungiasis.

### Implications for practice

The observed superiority of the intermittent application of Zanzarin repellent in preventing reinfestation by sand fleas makes it a feasible intervention. This repellent appears to be affordable and can probably be produced using local coconuts and *Aloe vera* even in resource-poor settings. Oral ivermectin cannot be recommended at this point owing to lack of good evidence on its efficacy against embedded sand fleas.

### Clinical scenario 53.5

A 45-year-old female is planning to travel to a country that is endemic for sand flies that transmit leishmania.

### What are effective topical preparations to reduce sand fly bites?

One RCT investigated the efficacy and safety of a soap composed of 20% DEET plus 0.5% permethrin repellent soap (Nopikex) in the prevention of sand fly bites (Table 53.7). Among the 18 volunteers, the coefficient of protection of this soap was 100% immediately after use versus 67% with placebo soap or no treatment. The knock-down action of the soap on sand flies, however, was not significant [63].

Table 53.7 Prevention of sand fly bites.

Ref.	Population	Species tested	Intervention	Comparisons	Outcomes	Main results	Study quality/Comments
Alexander et al. [63]	Valle de Cauca, Columbia N = 18 volunteers (9 assays)	<i>Lutzomyia youngi</i>	20% DEET + 0.5% permethrin repellent soap (Nopikex) Field study	Placebo soap No treatment	<ul style="list-style-type: none"> <li>• Coefficient of protection (CP)</li> <li>• Mortality of sand flies</li> </ul>	DEET + permethrin soap: CP immediately after use = 100% CP after 4 h = median of 44.3% Placebo soap vs no treatment: CP immediately after use = 67.7% (median) Mortality of flies within 24 h exposure – not significant Flies that fed on volunteers – not significant	Level 2 evidence DEET and permethrin soap had significant protection against sand fly bites immediately after use, lasting for 4 h, waning after 8 h, and no protection afforded after 12 h

### Drawbacks

Volunteers complained about the sticky, dry, or tight sensation of the skin after application. There were no reports of itching, tingling, or burning.

### Comments

Since this study had a small sample size, the evidence is inconclusive but shows a trend to benefit in favor of the DEET–permethrin soap.

### Implications for practice

The DEET–permethrin soap is affordable and does not react with plastic, unlike DEET-containing lotions. It is easy to apply but can be quickly rinsed off or removed when sweat is wiped off the skin. The consumer should reapply the soap on exposed skin, especially during the biting hours of the sand flies (i.e., within 2 h before sunset).

## Key points

### Mosquito bites

- We found fair evidence that 10 mg cetirizine may be taken prophylactically by adults to reduce the allergic skin reactions. Loratadine may be given prophylactically to children with allergies to mosquito bites when exposure to these insects is highly possible.
- We found fair evidence that topical ammonium sulfate solution may alleviate immediate burning, pain, and pruritus.
- We found fair evidence that dimethindene gel may relieve pruritus due to insect bites.
- We found good evidence that after-bite homeopathic gels tested have no significant benefit in persons with mosquito-bite allergy.
- We found no controlled clinical trials or RCTs that topical corticosteroids are effective in treating mosquito bites, although corticosteroids are commonly recommended for acute inflammatory skin reactions, including insect bites.
- We found good evidence that travelers to mosquito-endemic areas may achieve high levels of sustained protection against bites by using synthetic pyrethroid-treated patches and permethrin-treated clothing and tents.
- We found fairly reliable evidence that applying DEET only on exposed skin cannot effectively prevent mosquito bites, because bites can penetrate through untreated clothing. The mosquito-repellent efficacy and safety of alternatives to DEET have not been adequately assessed through RCTs.
- The combination of avoidance of the insects' habitats, barrier protection (e.g., clothing, bednets), and insect repellents are general measures for preventing insect bites.
- We found good evidence that DEET in a 20% solution form is reported to be safe for pregnant women in their second and third trimesters and does not result in adverse effects on their infants.

### Bee and wasp (Hymenoptera) stings

- We found fair evidence that honeybee stings should be removed immediately either by pinching, scraping, or other means in order to reduce the degree of envenomization.
- We found good evidence that ice packs or aspirin paste may reduce local swelling, pain, and pruritus, but that aspirin may prolong redness.
- We found no reliable evidence on emergency treatment specifically for systemic reactions to Hymenoptera stings. However, anaphylactic

reactions to insect venoms can be treated in the same way as anaphylaxis from any other cause. Sympathomimetics, antihistamines, and corticosteroids are the most effective drugs for dealing with systemic allergic reactions.

### Venom immunotherapy in preventing allergic reactions to insect stings

- We found good evidence that VIT is effective for preventing systemic allergic reactions to insect stings, for preventing large local reactions to insect stings, and for improving quality of life.

### Pretreatment with antihistamines in reducing the risk of adverse effects of venom immunotherapy

- We found good evidence that pretreatment with antihistamines such as cetirizine, fexofenadine, and terfenadine may reduce cutaneous adverse reactions to rush or ultra-rush VIT.
- Terfenadine with or without ranitidine may reduce systemic adverse reactions during the first 4 weeks of rush VIT.
- The efficacy of VIT is not affected by antihistamine premedication.

### Tick bites

- We found good evidence that topical repellents containing a combination of DEET and EBAAP (also known as IR3535) or lemon eucalyptus extract (citriodiol or PMD) may provide moderate protection against tick attachment.
- We found good evidence that education interventions are effective in the prevention of TBIs in areas that are endemic for Lyme disease and other TBIs.

### Sand flea bites (tungaiasis)

- We found good evidence that coconut oil, jojoba oil, and *Aloe vera* lotion (Zanzarin) is effective in treating tungaiasis of the feet and that the intermittent application of this lotion effectively prevents reinfestation of the feet by sand fleas.
- We found insufficient evidence that oral ivermectin is effective in clearing sand fleas embedded in feet.

### Sand flies

- We found fair evidence that 20% DEET plus 0.5% permethrin repellent soap provides good protection against sand fly bites immediately after use and up to 4–8 h.

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## SECTION 4: Disorders of pigmentation

Hywel C. Williams, editor

### CHAPTER 54

## Vitiligo

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### Background

#### Definition

Vitiligo is an acquired disorder of pigmentation mainly affecting the skin, in which the loss of functioning melanocytes results in white patches.

#### Incidence/prevalence

Vitiligo is a common skin disorder, affecting about 0.5% of the general population, irrespective of ethnic origin [1].

#### Etiology

There appears to be a genetic predisposition to vitiligo, consistent with a polygenic disorder. However, the pathogenesis of vitiligo still remains unknown. The main hypothesis theorizes an autoimmune process against melanocytes. Other theories include an intrinsic abnormality of melanocytes [2], toxic effect of free radicals [3], an increased release of catecholamines locally [4], and cytomegalovirus infection [5].

#### Prognosis

Although neither lethal nor symptomatic, the effects of vitiligo can be cosmetically and psychologically devastating. The course of the disease is fairly unpredictable, but often progressive [6].

#### Diagnosis

The diagnosis is clinical and based upon the presence of skin patches devoid of pigment.

#### Aim of treatment

The aim of treatment is to achieve partial or total repigmentation, at least for body areas that the patients estimate as “most significant,” with minimal adverse effects.

#### Relevant outcomes

- Physician-rated clinical response: success rate in terms of repigmentation (>75%) and long-term repigmentation rate.
- Side effects of treatment.

#### Methods of search

We searched for randomized controlled trials (RCTs) of currently available medical and surgical treatments at the Cochrane Central Register of Controlled Trials, Medline, and Embase, using the keyword “vitiligo.” The search was completed in June 2012. Where no RCTs were found, information from nonrandomized studies or case series was used.

A Cochrane systematic review (search date November 2009) and a *British Medical Journal* Clinical Evidence systematic review (search date March 2010) were used as a source of RCTs [7,8].

### Questions

#### What are the effects of medical treatment in vitiligo?

##### Case scenario

A 26-year-old woman reports a 10-year history of depigmented areas. Clinical examination reveals symmetrically distributed depigmented areas affecting the sun-exposed areas, mainly upper arms, face and neck (Figure 54.1).

##### Topical therapies

**Topical corticosteroids** One RCT [9] compared topical clobetasol propionate with psoralen plus sunlight therapy (PUVAsoL). Participants receiving clobetasol propionate were significantly more likely than those receiving PUVAsoL to achieve greater than 75% repigmentation (risk ratio [RR], 4.70; 95% confidence interval [CI],



Figure 54.1 Achromic areas on feet of a 35-year-old woman with vitiligo.

1.14–19.39). Another study [10] compared topical clobetasol propionate plus narrowband UVB phototherapy (NB-UVB) versus placebo plus NB-UVB. There was no statistically significant difference between the two groups. One RCT [11] compared topical hydrocortisone plus 308 nm monochromatic excimer light (MEL) versus MEL alone. Participants receiving the combination treatment were more prone to achieve 75% repigmentation than those receiving laser treatment alone (RR, 2.57; 95% CI, 1.20–5.50).

One RCT [12] compared topical betamethasone dipropionate with either calcipotriol or betamethasone dipropionate plus calcipotriol. None of the participants achieved greater than 75% repigmentation.

One RCT [13] found topical clobetasol to be more effective than topical pimecrolimus in the mean percentage of repigmentation (57.7% vs 32.1%, respectively;  $P < 0.05$ ) after 8 weeks of treatment.

One RCT [14] showed no statistically significant difference between topical clobetasol propionate and 0.1% tacrolimus with respect to repigmentation greater than 75%. One RCT [15] compared topical fluticasone propionate (FP) versus FP plus UVA phototherapy or versus UVA alone. No significant difference was seen between participants in the FP plus UVA group and those receiving FP alone in achieving greater than 75% repigmentation. FP alone and with UVA was superior to UVA alone (RR, 3.94; 95% CI, 1.16–13.43).

Topical class 3 corticosteroids have been shown to be effective in localized vitiligo, with a pooled odds ratio (OR) [16] of 14.3 (three RCTs [17–19]; 95% CI, 2.4–83.7); pooled ORs showed nonsignificant differences between topical class 4 or intralesional corticosteroids and their respective placebos [16].

One RCT [20] found that a combination of topical clobetasol and estrogen could be more effective than clobetasol alone in reducing the average area of lesions after 3 months' treatment ( $P < 0.001$ ).

**Drawbacks** All studies examining the effect of topical corticosteroids reported adverse effects, with the more frequent being atrophy, telangiectasia, hypertrichosis, and acneiform papules.

**Intralesional corticosteroids** One study [21] assessed the rate of adverse effects of triamcinolone acetonide injections versus placebo

injections and found atrophy in eight participants, telangiectasia in two, infection in one, and intradermal hemorrhage in one.

**Topical vitamin D analogues: calcipotriol and tacalcitol** Only one RCT [12] examined the effect of calcipotriol as monotherapy (see Topical corticosteroids section).

One RCT [22] compared calcipotriol plus PUVA with placebo plus PUVA. There was no statistically significant difference in the number of participants achieving greater than 75% repigmentation. One RCT [23] compared calcipotriol plus psoralen plus UVA phototherapy (PUVA) with placebo plus PUVA. The side of participants treated with the calcipotriol plus PUVA had a significant fourfold increase in the likelihood of achieving greater than 75% repigmentation sooner than the side treated with placebo plus PUVA (paired OR 4.25; 95% CI, 1.43–12.64). One RCT [24] compared tacalcitol plus MEL with placebo plus MEL. A statistically significantly greater proportion of participants in the tacalcitol plus MEL group achieved greater than 75% repigmentation (RR, 4.50; 95% CI, 1.05–19.35). Another RCT [25] compared tacalcitol plus sunlight versus placebo plus sunlight, but found no difference between the groups.

One study [26] found no significant differences between calcipotriol combined with NB-UVB and NB-UVB alone in achieving repigmentation of lesions.

One RCT [27] compared the effectiveness of NB-UVB alone and combined with tacalcitol. Addition of topical tacalcitol to NB-UVB improved the extent of repigmentation and increased the response rate.

**Drawbacks** The more frequent adverse effects associated with topical vitamin D analogues were mild skin irritation, xerosis (dryness), and itching.

**Calcineurin inhibitors: tacrolimus and pimecrolimus** Only one RCT [14] examined the effect of topical tacrolimus as monotherapy (see Topical corticosteroids section).

A meta-analysis [28] from two studies [28,29] found that topical 0.1% tacrolimus plus MEL was more effective than placebo plus MEL in achieving 75% repigmentation (RR, 3.15; 95% CI, 1.46–6.76).

One RCT [30] compared topical pimecrolimus plus NB-UVB versus placebo plus NB-UVB, finding no statistically significant difference in rates of repigmentation (RR, 3.38; 95% CI, 0.93–12.29).

One RCT [31] found pimecrolimus 1% cream and microdermabrasion to be more effective than pimecrolimus 1% cream alone in achieving more than 50% of pigmentation of the treated patches (60.4% vs 32.1%;  $P < 0.001$ ), over 3 months of follow-up.

**Drawbacks** The more frequent adverse effects associated with topical calcineurin inhibitor were burning sensations, erythema, and localized bullous eruptions.

The United States Food and Drug Administration has warned of a potential malignancy risk from the use of topical tacrolimus and pimecrolimus, principally based on the theoretical risk of immunomodulator utilization. A systematic review and a case-control study were not able to confirm such an association in individuals being treated for atopic eczema [32,33].

**Khellin** One RCT [34] compared the application of khellin in two different vehicles plus UVA versus the vehicles alone plus UVA.

There was no statistically significant difference in repigmentation between any intervention. No significant differences were found in a trial [35] that compared oral khellin and placebo plus sunlight.

**Pseudocatalase and catalase/dismutase superoxide** One study [36] compared Dead Sea climatotherapy plus pseudocatalase cream with Dead Sea climatotherapy plus placebo cream and Dead Sea climatotherapy alone. However, this study did not examine any outcomes of interest. One RCT [37] reported a self-limiting erythematous papular rash in one participant treated with a topical catalase/dismutase superoxide, but did not examine any other outcomes of interest.

**Melagenina (human placental extract)** One study [38] examined the effects of melagenina. However, the study examined no outcomes of interest.

**Comments/implications for practice** It appears reasonable to regard topical corticosteroids as the first-line treatment for localized vitiligo. Topical vitamin D analogues may be an alternative given in combination with light therapies.

Topical tacrolimus seems to be a useful tool, especially for the management of facial skin or eyelid lesions, where the risk of skin atrophy from topical corticosteroids or phototoxicity from phototherapy could be high.

No clear recommendations on the use of khellin, pseudocatalase and catalase/dismutase superoxide, and melagenina can be made on the basis of the current evidence.

### Oral therapies

One RCT [39] examined the effect oral *Ginkgo biloba*, compared with placebo. Overall, *Ginkgo biloba* showed a significant improvement over placebo (RR, 4.40; 95% CI, 1.08–17.95).

One RCT [40] compared the effect of oral minipulses of betamethasone (OMB) with three different combinations of interventions: OMB plus PUVA; OMB plus NB-UVB, and OMB plus broadband UVB phototherapy. There was a statistically significant difference in favor of OMB plus NB-UVB compared with OMB alone (RR, 7.41; 95% CI, 1.03–53.26), but not for OMB plus PUVA versus OMB alone or for OMB plus broadband UVB phototherapy versus OMB alone.

One RCT [41] compared oral azathioprine plus PUVA versus PUVA alone. The combination scheme was statistically significantly more likely to achieve greater than 75% repigmentation (RR, 17.77; 95% CI, 1.08–291.82).

One RCT [42] compared an oral antioxidant pool plus NB-UVB with NB-UVB alone. No statistically significant difference was found between the two groups.

Two RCTs [43,44] found no differences in a quality-of-life index between the use of *Polypodium leucotomos* plus NB-UVB and placebo plus NB-UVB, or between the use of oral levamisole plus topical mometasone furoate and oral placebo plus topical mometasone.

One RCT [45] compared the effectiveness of oral L-phenylalanine, with and without UVA. There was no statistically significant difference between the L-phenylalanine plus UVA group and the no active treatment group, or between the L-phenylalanine alone group versus the no active treatment group.

One RCT [46] compared oral vitamin B12 and folic acid plus NB-UVB with NB-UVB alone. The addition of vitamin B12 and folic acid did not improve any outcome.

**Drawbacks** Nausea was reported with L-phenylalanine, NB-UVB plus *Polypodium leucotomos*, and *Ginkgo biloba*. Weight gain was reported in subjects treated with minipulses of betamethasone.

**Comments/implications for practice** Systemic corticosteroids are not recommended, not only because of the limited evidence of their effectiveness, but also because of the wide range of adverse effects associated with them.

More long-term studies are needed in order to establish the effectiveness and safety profile of oral *Ginkgo biloba* and the possible additive effect of azathioprine when used with light therapies.

No clear recommendations on the use of oral antioxidants or levamisole can be made on the basis of the current evidence.

### Light therapies

**Oral psoralen plus ultraviolet A** There was no statistical difference in repigmentation in participants treated with PUVA compared with NB-UVB [47].

One RCT assessed PUVA in combination with calcipotriol [23] (see Topical vitamin D analogues section). One RCT assessed oral PUVA in combination with azathioprine [41] (see Topical vitamin D analogues section).

**Drawbacks** The more frequent adverse effects associated with PUVA were sedation, xerosis, erythema, exacerbation of acne lesions, and nausea.

**Psoralen plus sunlight therapy** One RCT [48] compared different psoralen compounds, doses, and combinations, combined with exposure to sunlight. One RCT [49] compared oral trimethylpsoralen (TMP) plus sunlight/sun lamp with placebo and the same light exposure in children. One study [50] compared oral PUVAsoL versus topical PUVAsoL versus oral triamcinolone combined with PUVAsoL. One RCT [22] compared topical calcipotriol plus PUVAsoL with placebo combined with PUVAsoL (see Topical vitamin D analogues section). One RCT [40] evaluated OMB plus PUVA, OMB plus NB-UVB, OMB plus BB-UVB, or OMB alone (see Oral therapies section); and one RCT [51] assessed minipunch grafting plus PUVAsoL versus split-skin grafting plus PUVAsoL.

Only two of the numerous comparisons of different psoralen compounds combined with exposure to sunlight were statistically significant and were based on data from one trial [48]: methoxypsoralen plus TMP versus psoralen plus sunlight (RR, 0.35; 95% CI, 0.14–0.87) and methoxypsoralen plus sunlight versus psoralen (RR, 2.50; 95% CI, 1.06–5.91).

**Drawbacks** Adverse effects reported were nausea, pruritus, dizziness, headaches, eye discomfort, and vague gastrointestinal symptoms. There was no evidence of liver or blood toxicity in either group.

**Ultraviolet A** See Topical corticosteroids section.

**Drawbacks** One RCT [15] reported a mild atrophy in areas treated with UVA.

**Ultraviolet B** In one RCT [52] none of the 10 participants receiving either NB-UVB or BB-UVB showed greater than 75% repigmentation after 12 weeks of treatment.



In another RCT, there were no statistical differences in repigmentation in participants treated with MEL from those treated with NB-UVB [53].

In one study, the combined therapy (5-fluorouracil plus Er-YAG laser plus NB-UVB) showed more repigmentation than NB-UVB phototherapy alone (RR, 5.60; 95% CI, 2.31–13.59) [54].

The outcomes for other studies are listed in the Oral therapies section [40,42,46], the Topical corticosteroids section [10], and the Calcineurin inhibitors section [30].

One RCT [55] found no significant differences in repigmentation between NB-UVB light plus a topical formulation including *Cucumis melo* superoxide dismutase and catalase (Vitix), and NB-UVB light alone.

One RCT [56] found no significant differences in repigmentation between pseudocatalase cream and NB-UVB versus placebo and NB-UVB.

One RCT [57] found no significant differences in repigmentation between NB-UVB, topical pimecrolimus, and tacrolimus.

One RCT [58] found no differences in degrees of repigmentation between targeted NB-UVB plus topical tetrahydrocurcuminoid versus targeted NB-UVB alone.

One RCT [59] compared the efficacy of topical PUVA versus NB-UVB. The treatment with NB-UVB was as efficient as with topical PUVA and had fewer adverse effects.

**Drawbacks** Adverse effects associated with UVB phototherapy were itching, hyperpigmentation and mild phototoxic effects.

**Lasers** One RCT [60] evaluated three different regimens of MEL. Repigmentation initiation correlated with treatment number, regardless of frequency. However, repigmentation occurred earlier in the most frequently treated lesions ( $P = 0.0336$ ).

Laser therapies associated with tacrolimus [28,29] (see Calcineurin inhibitors section), topical calcipotriol [61] (see Topical vitamin D analogues section), and topical hydrocortisone [11] (see Topical corticosteroids section) were evaluated.

Three RCTs evaluated percentage of repigmentation >75% [28,29] (see Calcineurin inhibitors section) [11]; (see Topical corticosteroids section).

One RCT [62] found that a combination of MEL and topical 1% pimecrolimus was more effective than only MEL in achieving repigmentation.

**Drawbacks** Laser therapy was associated with burning and/or stinging, moderate to severe erythema, blisters, and edema.

**Comments/implications for clinical practice** On the basis of the current evidence it appears reasonable to regard NB-UVB – alone or plus tacalcitol – as the first-line treatment for moderate to severe generalized vitiligo.

Treatment with MEL, alone or in combination with topical vitamin D analogues, tacrolimus, or topical corticosteroids, seems reasonable according to current evidence, but its utilization may be reduced because of its availability.

### **Surgical interventions**

**Suction blister grafts** One RCT [63] compared suction blister grafts with thin split-thickness grafts. Although repigmentation rates were compared, the study did not assess the primary outcome greater than 75% repigmentation. The only outcome of interest was adverse effects.

In another RCT [64], participants either underwent transplantation of cultured autologous melanocytes plus PUVA therapy (CMP) on one limb and PUVA only (PO) on another, or suction blister transplantation plus PUVA (SBP) on one limb and cryotherapy plus PUVA (CP) on another (see Oral psoralen plus ultraviolet A section).

**Punch grafts, minigrafts, and split skin grafts** One RCT [51] assessed minipunch grafting plus PUVAol versus split-skin grafting plus PUVAol. One study [65] made a five-way comparison between autologous skin minigraft plus 8-methoxypsoralen, minigraft plus placebo, minigraft alone, 8-methoxypsoralen alone, and placebo alone. No outcomes of interest were addressed and no adverse effects were reported. One RCT [66] compared pigmentation spread resulting from the use of a topical corticosteroid (0.1% fluocinolone acetonide) after punch grafting versus PUVA therapy after punch grafting (see Topical corticosteroids section).

One systematic review was found [67], based on case series only (a total of 39 series, reporting on five different techniques). The highest success rates occurred with split-thickness grafting and suction blister epidermal grafting, with 87% of patients achieving >75% repigmentation (sample-size weighted averages; 95% CI, 82–91 and 83–90, respectively). With minigrafting, 68% of the patients (95% CI, 62–64) were successfully grafted. A trial comparing minigrafting and suction blister epidermal grafting [68] confirmed the results of the review, although the outcome measure was the proportion of patches rather than the proportion of patients.

In a placebo-controlled trial including 18 patients, the addition of a melanotropin analogue applied topically on minigrafted patches did not improve the success of the minigrafting [69].

**Drawbacks** Cobblestoning, superficial scarring, and variegated appearance were associated with the minipunch grafting group. In the split-skin grafting group, superficial scarring was observed in all cases, as also were hypertrophic scarring, depigmentation, tire-pattern appearance, milia formation, and rejection of grafts.

**Melanocyte transplantation** One RCT [70] assessed a technique involving transplantation of epidermal cell suspension obtained from a skin graft. No statistically significant difference was found between the groups with respect to the number of participants achieving greater than 75% repigmentation.

**Drawbacks** The only adverse effect reported [70] was one case of bacterial infection at the recipient site.

**Comments/implications for practice** The data on surgical procedures should be interpreted with caution, as they are derived mainly from small case series and only scarce comparative trials, with questionable designs and outcome measures.

### **Psychological therapy**

One RCT [71] compared cognitive-behavioral therapy with person-centered therapy and also with controls receiving no psychological therapy. A total of 45 participants were enrolled. The study did not assess any other outcomes of interest.

**Comments/implications for clinical practice** Studies that take into account the effects of treatments on the patients' quality of life and global health, from the patient's point of view, are needed.

## Key points

- A meta-analysis, one additional systematic review, and several subsequent RCTs showed that NB-UVB, psoralen plus UVA light (using sunlight or artificial light sources), and topical class 3 corticosteroids are effective in comparison with placebo in treating generalized and localized vitiligo.
- There is RCT evidence indicating that NB-UVB is at least as effective as PUVA in achieving repigmentation of treated lesions.
- RCTs have reported that concurrent topical calcipotriol potentiates the efficacy of PUVA, but not the efficacy UVB. However, the concurrent use of topical tacalcitol has been shown to increase the efficacy of NB-UVB.
- There is some RCT evidence that indicates that tacrolimus is as effective as topical clobetasol propionate in treating vitiligo, although no placebo-controlled trials were found. Evidence from one RCT indicates that topical pimecrolimus is not effective in treating vitiligo.
- There is scarce RCT evidence on the efficacy of melagenine, pseudocatalase, levamisole, and systemic antioxidant therapy.
- We found limited evidence of the effectiveness of surgical treatments for selected patients
- We found that treatments were evaluated mainly in the short term, with few comparative trials. The maintenance value of therapies and the assessment of patients' preferences, satisfaction, and quality of life have not yet been adequately addressed. Patient compliance is seldom reported in the studies.

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## Background

### Definition

Melasma is an acquired increased pigmentation of the skin, characterized by grey–brown symmetrical patches, mostly on the areas of the face exposed to the sun, but occasionally on the neck and forearms [1]. Its clinical and histological presentation does not differ between men and women, apart from differences in the incidence (see below) (Figure 55.1).

### Incidence/prevalence

There are few studies showing the prevalence of melasma. A study conducted in Mexico [2] and another in Peru [3] found that melasma accounted for 4–10% of new dermatology hospital referrals. Melasma was found to be the third most common pigmentary disorder of the skin in a survey of 2000 black people at a private clinic in Washington, DC [4]. Melasma is thought to be more common in people of Hispanic origin who live in areas of high ultraviolet-light exposure, as well as in Asian people [5]. Melasma may also affect men, especially those of Hispanic or Asian origin.

### Etiology

Melasma occurs most commonly during pregnancy, and has also been associated with the use of oral contraceptives containing estrogens and/or progestogens, and with certain drugs such as hydantoin used as an anticonvulsant [6–8]. Sun exposure appears to be important for the development of melasma [9], and there also appears to be a familial predisposition [9]. On the basis of a small case series in Puerto Rico, sunlight exposure and family history appear to be the most important determinants for the development of melasma in men [10]. The exact cause of melasma is unknown; hormonal mechanisms may be involved. Mild ovarian dysfunction has been considered as a cause, after a study found increased levels of luteinizing hormone and low levels of serum estradiol in nine women with melasma [11]. A case–control study of 108 nonpregnant women with melasma found a significant association with increased thyroid antibodies in the blood [12]. Studies measuring

levels of immunoreactive  $\beta$ -melanocyte stimulating hormone found normal levels in patients taking oral contraceptives, some of whom had melasma [13], suggesting that the development of melasma is not related to melanocytic hormone.

### Prognosis

Melasma usually persists for several years. It may present as odd streaking on the face, causing cosmetic disfigurement, and can have a significant impact on the patient's quality of life [14]. Pregnancy-related melasma may persist for several months after delivery, and melasma related to hormonal treatments may persist for long periods after oral contraceptives have been stopped. Recurrences are common, particularly after repeat exposure to the sun [9]. The response to treatment can be variable, although dermal-type melasma is less responsive than the epidermal type (see below). The benefits of treatment may not be apparent for many months. Treatment is often unsatisfactory, and has been associated with side effects such as local irritation, scarring, contact dermatitis, and residual patches of lighter color on the skin – known as “confetti pigmentation.”

### Diagnostic tests

Melasma is a clinical diagnosis. Microscopy studies suggest that there may be two main types of melasma: the epidermal type, characterized by increased melanin pigmentation in the suprabasal layers of the epidermis; and the dermal type, characterized by increased melanin in the dermal macrophages, with associated milder epidermal hyperpigmentation [9]. This distinction may provide a clue to the expected treatment response. The dermal type has been found to be less responsive to conventional therapy [5]. An alternative way of establishing the type of melasma clinically is by using a source of ultraviolet A light, such as a Wood's lamp [15], in which the dermal type appears much darker than the epidermal type. Ultraviolet-light lamps enhance the lesions in light-colored skins (i.e., skin phototypes I–IV) [12], but may be of little use in dark-skinned people, in whom the enhancement is less prominent. This distinction may not be clinically relevant as most studies which





Figure 55.1 Patient with melasma.

perform this classification show the majority of these patients having epidermal or mixed-type melasma, with dermal melasma only present in 10% of patients [16]. This situation is further complicated by a study comparing clinical and histological examination by Grimes *et al.* which found that there was poor correlation between clinical examination with a Wood's light diagnosis of epidermal melasma and histological examination, as samples examined had increased melanin deposition in the epidermis and dermis [17].

### Aims of treatment

Treatments should aim to prevent the development of melasma, to prevent or reduce the severity of recurrence, to reduce the affected areas, improving the cosmetic defect, and to reduce the time to clearance, with the fewest possible side effects. The time to clearance is important, as current treatments take several months to have any effect.

### Relevant outcomes

- Improvement in patient satisfaction measures and quality-of-life assessment measures (Box 55.1) [14] during the time course of the intervention.
- Clearance of lesions as evaluated by objective methods; for example, the melasma area and severity index (MASI) or the melasma area and melanin index (MAMI) (Box 55.2) [18,19], or any other objective, semiquantitative measures of disease.
- Lightening of pigmentation (evaluated objectively by a colorimeter or a mexameter, for example).
- Adverse effects, such as irregular pigmentation or irritation related to the interventions.

### Methods of search

Medline (1966–April 2012), Embase (1980–April 2012) and the Cochrane Library were searched for the terms “melasma,”

#### Box 55.1 Melasma quality-of-life scale [14]

On a scale of 1 (not bothered at all) to 7 (bothered all the time), patients rate how they feel about:

- the appearance of the skin condition;
- frustration about the skin condition;
- embarrassment about the skin condition;
- feeling depressed about the skin condition
- the effects of the skin condition on interactions with other people (e.g., interactions with family, friends, close relationship);
- the effect of the skin condition on their desire to be with people;
- the skin condition making it hard to show affection;
- skin discoloration making them feel unattractive to others;
- skin discoloration making them feel less vital or productive;
- skin discoloration affecting the sense of freedom.

The melasma quality of life is scored from 7 to 70, with higher scores indicating a poorer melasma-related, health-related quality of life.

#### Box 55.2 Melasma scoring indexes

##### Melasma area and melanin index (MAMI) [18]

This is calculated in the same way as MASI (see below), but darkness and homogeneity are replaced by the single variable of the melanin index. This variable is a measurement of color at involved sites, determined using a reflectance spectrophotometer.

##### Melasma area and severity index (MASI) [19,20]

The index evaluates four areas of the face: the forehead (f), the right malar (rm) and left malar (lm) regions, and the chin (c). Each of the first three is weighted with 30% of the score, while the chin is weighted with 10% of the score. The extent of melasma in each area *A* is calculated and given a numerical value as follows:

0 No involvement

1 <10%

2 10–29%

3 30–49%

4 50–69%

5 70–89%

6 <90–100%.

The *severity* of the melasma is described by a combination of two factors, darkness *D* and homogeneity *H*, each evaluated on a scale of 0 to 4, and is calculated as follows:

$$\text{MASI} = 0.3(D_f + H_f)A_f + 0.3(D_{rm} + H_{rm})A_{rm} + 0.3(D_{lm} + H_{lm})A_{lm} + 0.1(D_c + H_c)A_c$$

where “f” is forehead, “rm” is right malar, “lm” is left malar, and “c” is chin.

“chloasma,” and “mask of pregnancy” as text words and/or key words if present in the database. Systematic reviews were searched for first, followed by randomized controlled trials (RCTs) using a filter; the remaining abstracts from the search were then scanned to see whether any RCTs had been missed using the search filter. References from identified papers were searched. The results of the search were appraised by at least two of the authors.

Categorization of studies: in most studies of melasma, sunscreens are used as a baseline measure with additional interventions. We have therefore not categorized them as combination studies. We

have used the term “combination study” when a combined effect of two or more interventions is assessed.

## Questions

### How effective are preventive interventions in high-risk populations?

#### Case scenario 55.1

A Latin-American woman is planning to have children and is concerned about developing melasma. Her three sisters all developed melasma during pregnancy, which lasted for many years.

#### Efficacy

We found no studies assessing the effects of preventive measures (such as educational interventions to avoid sun exposure or use of prophylactic sunscreens) in high-risk populations.

#### Comment

Overall, expert opinion supports interventions aimed at reducing exposure to ultraviolet light, which may reduce the risk of developing melasma.

#### Key messages

We found no good evidence to support preventive interventions in high-risk populations. Current opinion, based on known risk factors, suggests that preventing exposure to ultraviolet light such as sunlight may reduce the risk of developing melasma.

#### Implications for clinical practice/categorization

Unknown effectiveness.

### How effective are therapeutic interventions in childbearing, pregnant, and breastfeeding women who develop melasma?

#### Case scenario 55.2

A 30-year-old woman develops melasma in the 20th week of her first pregnancy. She is not on any medication and has not used an oral contraceptive in the past.

#### Efficacy

We found no studies in pregnant or breastfeeding women. Several studies did not clearly specify whether the women included were pregnant or became pregnant during follow-up. When components used in the study included those that are not recommended in childbearing women (i.e., retinoids), the study was considered to be done in nonpregnant or nursing populations and is discussed under the corresponding question.

#### Comment

Common expert opinion is that women with a high risk of developing melasma should avoid exposure to the sun or other sources of ultraviolet light. It would seem reasonable to consider the use of broad-spectrum sunscreen with solar protection factor (SPF) >30 in women who are at high risk of developing melasma.

#### Key messages

We found no good evidence to support any therapeutic intervention in childbearing, pregnant, or breastfeeding women. Current opinion suggests that such women with melasma may benefit from

using broad-spectrum sunscreens and avoiding exposure to ultraviolet light such as sunlight.

#### Implications for clinical practice/categorization

Unknown effectiveness.

### How effective are therapeutic interventions in non-childbearing women?

#### Case scenario 55.3

A 35-year-old woman presents with a 3-month history of melasma. She had been taking an oral contraceptive, which she had recently stopped taking after a tubal ligation. She is an outdoor worker.

#### Sunscreens

##### Efficacy

We found one systematic review [21]. We found one RCT [22] comparing sunscreens with placebo in women receiving hydroquinone. The study included 59 nonpregnant Hispanic women in Puerto Rico. None of the participating women was taking contraceptive hormones and all had had melasma for 2–25 years. All of the women were prescribed a clearing solution of hydroquinone 3% in hydroalcoholic solvent twice daily. The women were randomly assigned to a once daily morning application of broad-spectrum sunscreen or vehicle (placebo) and were then followed for 3 months. Improvement, assessed subjectively by a physician, was seen in 26 of 27 (96%) women receiving sunscreen and hydroquinone, in comparison with 21 of 26 (81%) women receiving placebo and hydroquinone (relative risk [RR], 1.19; 95% confidence interval [CI], 0.98–1.46). Improvement rates as assessed by participants were high in both groups: 27 of 27 (100%) with sunscreen and hydroquinone, in comparison with 25 of 26 (96%) with placebo and hydroquinone (absolute risk reduction [ARR], 4%; 95% CI, 1–18.9%). Six of the 59 (10%) women withdrew and nine of 53 (17%) women developed side effects of stinging and burning.

##### Comment

The side effects seen in the nine patients above were attributed to hydroquinone. It is unclear which arm this was in as both groups received hydroquinone.

##### Key messages

We found limited evidence from a single RCT evaluating the effect of therapeutic sunscreens. It showed that, during the 3-month follow-up period, the majority of women receiving hydroquinone improved regardless of the addition of sunscreen to their treatment. There was no detail, for example, of the SPF of the sunscreen or if participants could reapply the sunscreen during the day. The study also did not describe if women used other strategies to avoid sunlight. Sunscreens are commonly a co-intervention in studies on melasma and improvements seen in the placebo arm ascribed to the sunscreen co-intervention.

#### Implications for clinical practice/categorization

Unknown effectiveness.

#### Topical corticosteroids

##### Efficacy

We found one systematic review [21] and one trial of 17 participants (16 consecutive women and one man) followed for 3 months

[23]. The trial compared the topical application of a 0.2% betamethasone 17-valerate cream with cream excipient (placebo). Randomization was used to allocate the side of the face to which creams were applied. There was good improvement (subjectively defined by the physician and participants) in eight people, eight of whom considered betamethasone to be better than placebo. Three considered they achieved moderate improvement with either betamethasone or placebo, and four people said they had no improvement at all. One person withdrew from the trial.

### Drawbacks

The study reported no significant side effects [23].

### Comment

Although the study reports that betamethasone was effective as a depigmenting agent ( $P < 0.05$ ), the numbers were very small and seven of 16 patients found no therapeutic difference between treatment and placebo [23]. There is controversy over the balance between benefits and harms of using topical steroids in the treatment of melasma, especially since long-term use on the face can cause skin thinning and telangiectasia.

### Key messages

We found insufficient evidence to support the use of topical steroids in melasma. There is controversy over the use of topical steroids in melasma.

### Implications for clinical practice/categorization

Unknown effectiveness.

### Topical retinoids

#### Efficacy

We found one systematic review [21] and three RCTs.

**In Caucasian people** The first RCT was done in 50 Caucasian women with facial melasma (94% epidermal, 4% dermal, 2% mixed) [24]. The trial compared the daily use of topical 0.1% tretinoin with placebo (vehicle cream for tretinoin) over a period of 40 weeks. The withdrawal rate was 24%. At 40 weeks there was a significant difference and 13/19 in the tretinoin group were rated as “improved” or “much improved” compared with 1/19 in the placebo group ( $P = 0.0006$ ).

**In Asian people** The second RCT [18] included 30 Thai people (26 women and four men) with facial melasma. The RCT compared a titrated daily application of 0.05% isotretinoin gel with a color-matched vehicle used as placebo, for 40 weeks. There were no significant differences in the MASI or MAMI scores in the evaluations done at 2 weeks, 4 weeks, and monthly for up to 40 weeks. The only two participants with dermal melasma were allocated to the isotretinoin group. Participants in both groups improved during the 40-week follow-up.

**In black people** One RCT in the USA compared the daily application to the entire face of a cream with 0.1% tretinoin or placebo (vehicle) in 30 Afro-Americans (29 women), followed for 40 weeks [19]. The MASI score was used to assess the severity of melasma. Darkness and homogeneity were also assessed. Colorimetry, photographic, and histology studies were carried out before and after

treatment. After 40 weeks, there was a mean reduction in the MASI score by 32% compared with a mean reduction in the placebo group by 10% ( $P = 0.03$ ). The significant improvement noted on the subjective MASI evaluation was also confirmed on colorimetry. This improvement, however, was not seen on all measures. Patients were also assessed by an independent clinician, who found no significant differences between tretinoin and placebo after 24 weeks – improved or much improved: 11 of 15 (73%) with tretinoin, compared with six of 13 (46%) with placebo (RR, 1.6; 95% CI, 0.8–3.1).

### Drawbacks

**In Caucasian people** In the first RCT, 12 participants were lost to follow-up. One of the causes for withdrawal was adverse events in the tretinoin group: three of 25 (12%) versus none of 25 with placebo. Worsening of melasma occurred in a woman in the tretinoin group. Moderate cutaneous reactions were more frequent with tretinoin (22 of 25; 88%) than with placebo (seven of 24; 29%; RR, 3.0; 95% CI, 1.6–5.7). The number needed to harm (NNH) was 1.7 (95% CI, 1.3–3.1). Severe cutaneous reactions occurred only with tretinoin (four of 25; 16%; NNH, 6.3) [24].

**In Asian people** The second RCT found similar withdrawals rates in both groups: four of 15 (27%) with isotretinoin, in comparison with three of 15 (20%) with placebo [18]. Mild transient erythema and/or peeling occurred only in the isotretinoin group (four of 15; 27%; NNH, 3.8), which resolved after 4 weeks.

**In black people** The most frequently found side effects in the third RCT were erythema and/or peeling in the area of application: 10 of 15 (67%) with tretinoin, in comparison with one of 15 (7%) with placebo (RR, 10; 95% CI, 1.5–68.7; NNH, 1.7; 95% CI, 1.1–2.4) [19].

### Comment

The withdrawal rate was high in the first RCT on Caucasian patients and there was no intention-to-treat analysis [24]. All three RCTs have small samples, and are inconclusive as a result. The RCT on black patients showed no significant improvement on the scale of “much worse” to “much improved,” but when the MASI scores were analyzed a significant difference was detected [19]. Side effects were quite common in people receiving retinoids.

### Key messages

We found some evidence of an effect of retinoids in people with melasma, and more so in Caucasian patients with a higher proportion of epidermal melasma over black patients with dermal melasma. No beneficial effect was observed with topical isotretinoin, a chemically related structure to tretinoin.

### Implications for clinical practice/categorization

Tretinoin may be beneficial.

### Azelaic acid

#### Efficacy

We found one systematic review [21] and three RCTs.

The first RCT [25] was a prospective, single-blinded study in 30 Indian patients (25 females, five males) that compared 20% azelaic acid (AZA) versus 20% AZA and 0.05% clobetasol propionate used sequentially. This was a left-to-right comparative study, with 20% AZA used on one side for 24 weeks, in comparison with 8 weeks

of topical steroid followed by 16 weeks of 20% AZA. Clinical evaluation, photographic controls, and an assessment for overall response were done at 4, 8, 16, and 24 weeks. Evaluations done at 4-weekly intervals showed improved outcomes at 16 weeks with sequential therapy in comparison with 20% AZA alone ( $P > 0.001$ ). However, at week 24, both groups showed good to excellent responses.

We found two RCTs [26,27] comparing AZA with hydroquinone. The first compared 20% AZA with 2% hydroquinone [28] and the second with 4% hydroquinone [26]. Most studies of hydroquinone have used the 4% strength, and the study using 2% hydroquinone did so as there were ethical obstacles to using placebo. The first RCT [28] was in 340 patients with epidermal or mixed melasma (including 17 men) comparing twice-daily 20% AZA cream with twice-daily 2% hydroquinone cream for 24 weeks. It found that improvement (defined as a reduction of  $>50\%$  in a score including area and pigmentation) was higher with AZA (106 of 154; 69%) than with hydroquinone: 88 of 161 (55%) (RR, 1.26; 95% CI, 1.06–1.50), number needed to treat (NNT) 7 (95% CI, 4–30). The majority of patients were of skin phototypes III–VI. However, no statistical difference between the groups was found on the objective measures of reduction in lesion size. The second RCT [26] was on 329 South American women with epidermal or mixed melasma comparing twice-daily 20% AZA cream with twice-daily 4% hydroquinone cream for 24 weeks. There was no significant difference in the two groups with regard to overall response or reduction in pigmentary intensity. Both subjective and objective assessments were made. Using the participants who had good to excellent response as “treatment success,” 71.9% of those in the hydroquinone group had success versus 64.8% in the AZA group.

### Drawbacks

The RCT [25] comparing sequential therapy of AZA and topical steroids found little difference in adverse events between the groups. Five patients in the AZA group suffered mild irritation, while six patients in the sequential therapy group suffered mild acneiform eruptions. Sequential treatment produced faster improvement at 16 weeks, though there was no significant difference between the two groups at 24 weeks.

In both the comparison RCTs with hydroquinone, side effects were more frequent with AZA. In the first comparison RCT [28], mild adverse events including itching, burning, and erythema were reported in 61/147 in the AZA group and 22/153 in the hydroquinone group (RR, 3.0; 95% CI, 1.7–4.7; NNH, 4; 95% CI, 3–6). Marked irritation was more frequent with AZA (15 of 167; 9%) than with hydroquinone (two of 173; 1%; RR, 7.8; 95% CI, 1.8–33.5; NNH, 12; 95% CI, 7–30).

In the second RCT [26] most of the side effects were mild and transient, occurring more frequently in the AZA group (18/122) versus the hydroquinone group (1/121).

### Comment

The two studies [26,28] comparing AZA and hydroquinone reached different conclusions, and this is likely to be secondary to the different hydroquinone concentrations. There was a large loss to follow-up (86 participants out of 329) in the RCT comparing AZA with 4% hydroquinone [26], though the differential loss to follow-up between the groups was not significant. No intention-to-treat analysis was used. The use of topical steroids was associated with faster clearance, but has to be evaluated for side effects in larger studies.

### Key messages

We found some evidence for the use of AZA, which was found to be superior to 2% hydroquinone in achieving improvement. We found no difference when AZA was compared with 4% hydroquinone. AZA was associated with a higher incidence of side effects. When used sequentially with AZA, topical steroids may result in faster improvement of melasma.

### Implications for clinical practice/categorization

May be beneficial.

### Hydroquinone

#### Efficacy

We found one systematic review [21] and two RCTs. The first RCT [29] was done between autumn and spring in Brazil (48 patients, four men; age range 19–55 years). The trial compared a cream containing 4% hydroquinone and two sunscreens of SPF 15 with a cream containing two sunscreens of SPF 15, both applied for 12 weeks. In addition, participants applied an SPF 30 sunscreen every morning; no explanation was given for the need of three different sunscreens in each arm. Outcomes were assessed by subjective clinical evaluation and photography. After 12 weeks, hydroquinone showed higher improvement rates (20 of 21; 95%), in comparison with 16 of 24 (67%) with placebo (RR, 1.4; 95% CI, 1.06–1.9; NNT, 3.5; 95% CI, 1.9–12.1). Total clearance of lesions was more frequent in patients receiving hydroquinone (eight of 21; 38%) in comparison with placebo (two of 24, 8%; RR, 4.6; 95% CI, 1.1–19.2; NNT, 3.4; 95% CI, 1.8–12.7).

A second RCT [30] randomized women's hemifaces to receive once-daily 5% ascorbic acid versus once-daily 4% hydroquinone in 16 women with melasma in Mexico. All participants were also instructed to apply a sunscreen every 3 h in the day. The women were evaluated every 4 weeks using digital photography, colorimetry, and subjective assessment: mild ( $<25\%$ ), moderate (25 to  $<50\%$ ), good (50 to  $<75\%$ ) and excellent ( $>75\%$ ). The women rated clearance better in the hemiface that received hydroquinone, at 93% (good to excellent) versus 62.5% (good to excellent;  $P < 0.05\%$ ). No significant differences were found between the treatments in the colorimetry evaluation.

We found two RCTs comparing hydroquinone with AZA (see above) [26,28].

### Drawbacks

The first RCT [29] found no difference in tolerability between the groups. Adverse events, mostly erythema, were reported in six of the 21 of those in the hydroquinone and sunscreen group versus five of the 24 in the sunscreen-only group (RR, 1.37; 95% CI, 0.49–3.85). In the second RCT [30], irritation was more frequently seen in the side that received hydroquinone (irritated hemiface: 11 patients with 4% hydroquinone versus one patient with 5% ascorbic acid).

### Comment

Hydroquinone (4%) plus sunscreen was found to be superior to placebo plus sunscreen [29]. The difference between treatments was stated to be statistically significant, though it is unclear which category of improvement was analyzed (“total” or “partial improvement” categories). Outcomes were not reported in five patients. The second study found that 4% hydroquinone was superior to 5% ascorbic acid on the patients' subjective assessments, but this improvement was not seen with objective colorimetry assessment [30].



### Key messages

We found evidence from one RCT showing that the use of hydroquinone plus sunscreen was superior to the use of sunscreen and placebo. We found limited evidence of the efficacy of 4% hydroquinone over 5% ascorbic acid. Although no significant difference was found on colorimeter assessment, the participants who self-assessed favored hydroquinone.

### Implications for clinical practice/categorization

May be beneficial (when used with sunscreen).

### Acid peels

#### Efficacy

We found one systematic review [21] and eight RCTs.

The first RCT [31] was a small split-face study of 10 participants in Singapore (skin phototypes IV or V), suffering moderate to severe epidermal melasma. This split-face study compared glycolic acid (GA) peels (concentration 20–70% increased according to tolerability) applied every 3 weeks to one side of the face with GA and hydroquinone cream applied twice daily for 24 weeks to both sides of the face. All participants also had a pretreatment of twice-daily 8% alpha hydroxy acid skin smoothing cream for 2 weeks. An independent evaluator assessed the results using a Munsell color chart and photographs. Participants also assessed the results. The physician evaluation found improvement on the side using peeling in all cases, and improvement in control sides in eight of 10 cases.

The second RCT [32] was in 40 patients in Pakistan (30 women and 10 men, aged 21–45, with phototypes IV–V, with melasma). They were randomly divided into two groups of 20 each. They all had six fortnightly facial peeling sessions with increasing concentrations of salicylic acid (first two sessions with 20% and subsequently with 30%). Group I was also treated with 4% hydroquinone cream for the subsequent 3 months, but group II had no additional treatment. Both groups used broad-spectrum sunscreens. Evaluations were made before and after finishing treatment, including a MASI score, photographs, and lesion size. The use of chemical peelings with salicylic acid showed significant improvement in both groups ( $P < 0.05$ ). After an additional 3 months of treatment with 4% hydroquinone cream, 80% of the patients in group I were reported to have continued significant improvement, in comparison with 50% of those in group II ( $P < 0.05$ ).

The third RCT [33] was a split-face trial on 21 Hispanic participants with moderate to severe epidermal or mixed melasma in Texas, USA. Patients were randomized to receive either 4% hydroquinone cream or 4% hydroquinone cream and 20–30% GA peels every 2 weeks applied to either the right or left side of the face for 8 weeks. Eleven of 18 participants felt there was more improvement on the peeled side versus 4/18 on the nonpeeled side. One of the patients felt there was no difference between the sides. In this RCT, physicians assessed improvement with subjective and objective measures. While there was a significant improvement from baseline in both groups, there was no significant difference in improvement in MASI scores or objective mexameter readings.

The fourth RCT [34] was a trial to compare Jessner's (14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol) peel with 30% salicylic acid peel after 2 weeks priming with 0.05% tretinoin cream nightly. Sixty participants with epidermal melasma were randomized to receive either Jessner's peel or salicylic acid peel for 5 min every 2 weeks for 12 weeks. There was a subsequent 12-week follow-up period. The authors found no statistically significant dif-

ference between the groups in terms of reduction of MASI at 12 weeks or 24 weeks.

The fifth RCT [35] was a split-face trial on 16 Korean patients (skin type III or IV) with mixed melasma confirmed on Wood's lamp analysis. Both sides of the face were treated for six sessions at 1 week intervals with a Q-switched 1064 nm laser (MedLite C6; Hoya ConBio, Fremont, CA, USA) (6 mm spot size, fluence 2–2.3 J/cm<sup>2</sup> at 10 Hz). In addition, one side of the face was randomly allocated to receive three sessions of 30% GA at 2 week intervals immediately after laser therapy. All patients were given a broad-spectrum SPF 50 sunscreen. Both objective and subjective assessments were performed. At the completion of the sixth laser treatment the peeled side had a 32.6% reduction in melanin index from baseline versus 22.0% reduction in the laser only side ( $P < 0.05$ ). This significant difference was also noted on the modified MASI (calculated to account for a certain portion of the malar area), where the physicians recorded a 37.4% reduction in the modified MASI in the peeled side versus 16.7% in the laser-only side. There was also a 5-month follow-up period, and 75% of patients on the combined peel and laser therapy rated their treatment as good or excellent versus 38% on the laser-only side.

The sixth RCT [36], a right–left comparison study, evaluated the effect of GA solution (Glycolic Acid Peels, NeoStrata, Princeton, NJ) and amino fruit acid (AFA) gel (AFA Peels, exCel Cosmeceuticals, Bloomfield Hills, MI) on Turkish patients (skin types II, III (79%) and IV) with epidermal-type melasma determined with a Wood's lamp. Thirty-one patients received 12 serial peels at 2-week intervals for a period of 6 months with GA on one side and AFA peels on the other side of the face. Contact time (2–6 min) and concentration (20, 35, 50, 70% GA; 20, 30, 40, 50, 60% AFA) was gradually increased depending on tolerability. Patients used broad-spectrum sunscreen (SPF 30) and practiced strict sun avoidance during the treatment period. At baseline and months 3 and 6 a modified MASI score was performed, alongside cutaneous tolerability assessments during and after peeling sessions and patient preference tests at the end of the study period of 6 months. A significant reduction of modified MASI score ( $P > 0.05$ ) was found at 6 months with both peeling methods. (GA:  $4.66 \pm 3.33$  to  $2.937 \pm 2.10$ ; AFA:  $4.237 \pm 3.22$  to  $2.547 \pm 2.05$ ) When comparing the two peeling methods, however, the authors found no significant difference between end of treatment modified MASI scores or patients' preference tests regarding melasma improvement (GA: 45.8%; AFA: 41.7%; same: 12.5%) or choice for future treatment (GA: 41.7%; AFA: 54.27%; same: 4.2%).

The seventh prospective, randomized study [37] compared the efficacy of Jessner's solution versus trichloroacetic acid (TCA) 20% solution versus concomitant use of hydroquinone 2% and kojic acid 2% as two separate products applied together. Forty-five female patients (skin types III, IV) with epidermal and mixed melasma (identified with Wood's light) had been randomized in three groups. After 2 weeks' priming with retinoic acid 0.05% daily, groups A and B received chemical peeling with either Jessner's solution or TCA 20% weekly for six sessions. Group C used hydroquinone 2% and kojic acid 2% as two separate products applied together at night for 8 weeks. The study was carried out in winter and all patients used SPF 45 sunscreen. Outcome was measured using the MASI score detected by a blinded investigator. At baseline, MASI score showed no significant difference between the three different groups and was as high as 13.660, 12.207, and 14.5 respectively in groups A, B, and C. The MASI score decreased significantly in each group ( $P < 0.001$ ) at week 8. After a follow-up period of 16 weeks, the MASI scores

were raised in each group compared with week 8, but they were still significantly lower ( $P < 0.001$ ) than baseline. Comparing the three different groups, at week 8, the MASI score was significantly lower in group A (Jessner's) and group B (TCA) than group C (hydroquinone and kojic acid), but there was no significant difference between groups A and B. After the 16-week follow-up period the MASI score stayed significantly lower ( $P < 0.001$ ) than baseline, but there was also a statistically significant difference between each group, with group B being the lowest and group C the highest.

The eighth RCT [38] compared application of 4% hydroquinone with a combination of 4% hydroquinone and 20–30% salicylic acid peels. This study was on 20 Latin American females of skin types III–V. The study design was of split face and the comparison was done by narrowband reflectance spectrometry. There were a total of four peels done 2 weeks apart. The study period was 8 weeks. The authors did not find any significant differences between the two sides of the face.

### Drawbacks

All of the participants in the first RCT [31] experienced stinging and redness post-peel, which was transient. One person had a burn after the 20% GA peel, resulting in hyperpigmentation, which cleared in 2 months. No side effects in the nonpeeled group were mentioned in the text.

In the second RCT [32], minor side effects were seen in most of the patients, such as mild burning, irritation, and stinging. No information is available about three patients who did not finish the treatment.

In the third RCT [33], four participants developed significant erythema, though no peeling or erosions occurred secondary to peels. There was no comment on adverse events from hydroquinone.

In the fourth RCT [34], eight of the 34 participants had excessive crusting versus 10/26 in the salicylic acid group (four crusting, two sunburn, two pigmentation, and two acneiform eruption) (RR, 1.63; 95% CI, 0.75–3.55).

In the fifth RCT [35], limited detail (no numbers presented) of adverse events was provided. Side effects were stated to be transient and mild, including erythema, burning, and desquamation.

In the sixth RCT [36], three patients developed vesicles, crusting, and erosions on the GA-treated site, and no side effects were observed with AFA applications. The authors stated that tolerability of AFA was better, resulting in an overall greater application in higher concentration during the 12 sessions.

In the seventh study [37] there were no drop-outs during the 8 weeks' treatment and the 16-week follow-up period. Transient side effect (<2 weeks) with post-peeling erythema occurred in 30% of patients treated with Jessner's solution and 20% of patients treated with TCA. Discomfort was reported in 25% in both groups. Hyperpigmentation developed in 1/15 patients treated with Jessner's solution and 3/15 in the TCA group. No side effect was reported in the third group treated with hydroquinone and kojic acid.

In the eighth RCT [38], limited detail (no numbers presented) of adverse events was provided. Side effects were stated to be transient and mild, including erythema, burning, and desquamation. This study was limited to four salicylic acid peels and over a short period of time of 8 weeks.

### Comment

The first RCT may have been too small to rule out differences, and concealment may have been difficult to achieve because of the side

effects of the peelings [31]. The second RCT [32] has methodological flaws. There is no description of inclusion or exclusion criteria, methods of randomization, or description of concealment. Further evaluation in long-term studies with better methodological quality is necessary to evaluate side effects and recurrences.

In the third RCT, two of the 21 participants did not complete the global evaluation and the data presented were incomplete. There is also no clear record of the side effects from hydroquinone [33].

In the fourth RCT, only patients with epidermal melasma were included. There were three withdrawals at 12 weeks and 14 withdrawals (23.2%) at 24 weeks. No intention-to-treat analysis was performed [34].

In the fifth RCT [35] the baseline characteristics were not provided for each group, though it was noted there was no significant difference in the relative lightness index between the two sides of the face. Adverse events were reported in minimal detail, with a further statement that no new adverse events were noted. It is unclear if these were not recorded if the authors felt it was a known side effect of peels or lasers.

In the sixth RCT [36] only a small number of patients with epidermal melasma were included. The investigators followed an individualized treatment regime with different application times and concentrations which resulted in better tolerability, but it might have influenced overall outcomes. No follow-up was carried out after the 6-month treatment period.

In the seventh study [37] the authors found that TCA might be superior to Jessner's solution and hydroquinone applied with kojic acid in the long term, as relapse rate was lower in this group. However, a higher rate of postinflammatory hyperpigmentation occurred in this group. It is not clear if hyperpigmentation influenced the assessment of the MASI score in the TCA group.

The eighth RCT [38] is limited by a small number of participants and by the fact that only four peels were done in each patient.

### Key messages

We found insufficient evidence to assess the effects of acid peels, as a variety of concentrations and formulations were used in each study. Only two RCTs compared two different peels. These trials found no significant difference either between Jessner's and 30% salicylic acid peels or comparing GA with AFA peels. GA peels did not enhance the effect of hydroquinone cream as similar effects were noted with use of hydroquinone cream alone. Additionally, GA peels did not enhance the lightening effect when combined with hydroquinone and GA cream. GA peels did enhance the lightening effect of Q-1064nm laser in one RCT. This effect was maintained over the 5-month follow-up period, though a slight deterioration was noted. There was limited evidence of effectiveness of salicylic acid peels from one RCT, which showed significant improvement in the treated groups from baseline, the effect of which was augmented with 4% hydroquinone. This study had limitations. Studies with longer follow-up periods and better methodological qualities will be required. In the former three RCTs, increased adverse events were noted on the peeled side.

### Implications for clinical practice/categorization

Unknown effectiveness.

### Combined therapies

#### Efficacy

We found one systematic review and 11 RCTs. The first trial was an open RCT (50 Asians, 49 women, with nondermal melasma and

not taking oral contraceptives) [20]. It compared the daily use of a cream containing 20% AZA, 0.05% tretinoin, and sunscreen, with a cream containing 20% AZA and sunscreen, for a period of 6 months with monthly evaluations. The number of withdrawals was high and it is therefore difficult to draw conclusions. In addition, some outcome categories overlapped.

A second RCT [39], including 65 dark-skinned people with skin phototypes >III, with hyperpigmentation, 44 of whom (68%) had melasma, compared a cream containing 20% AZA cream plus 15–20% GA (first month only) plus sunscreen with 4% hydroquinone plus sunscreen; the participants were followed for 24 weeks. There was no difference between the two groups with regard to overall improvement, and the reductions in lesion area, pigmentary intensity, and disease severity were comparable in the two treatment groups.

A third RCT [40] was conducted on 40 Chinese women with pure epidermal melasma, confirmed by Wood's lamp (age range not specified), comparing a twice-daily application of a gel containing 2% kojic acid, 2% hydroquinone, and 10% GA followed by a sunblock with titanium dioxide SPF 15 with a twice-daily application of a control gel containing 2% hydroquinone and 10% GA, followed by sunblock with titanium dioxide SPF 15. Randomization was used to determine which side of the face would receive each intervention. The frequency of >50% clearance of the melasma area was greater on the kojic acid side, although the difference was not significant: 24 of 40 (60%) for the gel containing kojic acid, versus 19 of 40 (48%) for the combined gel without kojic acid (RR, 1.3; 95% CI, 0.8–1.9). When the participants assessed improvement, it was found to be better with the gel containing kojic acid.

The fourth RCT [41] included 38 women with skin phototypes I–IV and melasma (type not specified). The study randomized affected areas of skin instead of people, and randomization was carried out using a list. The study compared a cream containing 12% alpha hydroxyl acid (particular preparation not specified), 1% polypeptide ascorbate complex, and titanium oxide photoprotector with a preparation containing titanium oxide photoprotector and the vehicle for the cream prepared to the same pH. On the patients' global assessment, measured using a visual analogue scale (VAS) for area and pigmentation, more women receiving the active treatment improved than those using placebo. However, the difference did not quite reach significance; 34 of 36 (94%) with the combination treatment versus 17 of 36 (47%) with the placebo (RR, 1.51; 95% CI, 0.96–2.40). Differences were significant for the melanic index, measured using a mexameter (mean melanic index 15.2 with the active treatment versus 22.1 with placebo;  $P < 0.01$  at day 56).

The fifth RCT [42] (39 patients with facial melasma, 5% of whom had dermal melasma under Wood's light; 38 women, followed for 3 months) compared 2% hydroquinone and 5% GA gel with 2% kojic acid and 5% GA gel. This study compared interventions applied to the left or right side of the face. Outcomes involved a comparison of facial photographs taken using an ultraviolet filter, clinical evaluation, participants' impressions, and the decrease in the affected area (no formal scales were used). There were no significant differences between the groups (28% reduction with kojic acid and 21% reduction with hydroquinone).

The sixth RCT [43] compared 4% hydroquinone cream plus 10% buffered GA, plus vitamins C and E plus sunscreen (compound cream, concentrations of vitamins C and E unspecified) versus sunscreen cream alone over a period of 12 weeks in 39 Hispanic women with epidermal melasma, skin types III–V, aged 18–50 years. Improvement in pigmentation was assessed objectively using the

mexameter and subjectively with MASI assessments. There was a significant decrease in the mexameter readings ( $P < 0.0001$ ) and reduction in MASI ( $P < 0.01$ ) using the combination cream compared with sunscreen alone. However, the patients' global evaluation showed moderate, obvious, or marked improvement in 19 of 20 women (95%) using the combination cream and 13 of 15 (87%) with sunscreen alone.

The seventh study [16] was a multicenter trial that included 641 patients who were randomly assigned to receive either tretinoin 0.05% (RA), hydroquinone 4.0% (HQ), and fluocinolone acetonide 0.01% (FA) (RA+HQ+FA) in a hydrophilic cream base; or (RA+HQ) or (RA+FA) in the same vehicle cream. A baseline photograph, an eight-point scale for investigator assessment of global improvement, and a melasma severity rating score (0–4) were used. The patient population consisted predominantly of white women, with skin types I–IV. The patients included had had melasma for at least 3 months and had a melasma severity of at least 2 on the melasma severity score. The end point of the study was the proportion of patients achieving complete clearance at 8 weeks. A secondary end point was the proportion of patients achieving complete or near-complete clearing (severity rating score: 0). At 8 weeks, the authors found that 26.1% of the patients were completely cleared with RA+HQ+FA, in comparison with 9.5% with RA+HQ, 1.9% with RA+FA, and 2.5% for HQ+FA ( $P < 0.001$ ). Complete clearing or near-complete clearing was achieved in 77% of patients in the RA+HQ+FA group, in comparison with 42.2% for HQ+FA, 27.3% for RA+FA, and 46.8% for RA+HQ ( $P < 0.001\%$ ).

The eighth RCT [44] was a multicenter trial in nine centers in South East Asia on 260 participants who were randomized to triple-combination (RA+HQ+FA) cream or 4% hydroquinone cream for 8 weeks. Participants assessed self-improvement using a static global assessment score. A score of 0 related to clear and 1 related to minor hyperpigmentation. Significantly more participants in the triple-combination group (87/125) compared with the 4% hydroquinone group (57/129) achieved a score of 0 or 1 (RR, 1.58; 95% CI, 1.26–1.97). This significant difference was also noted in the physician assessment. In this trial the participants' overall satisfaction with treatment was assessed by means of a questionnaire. Significantly more participants (71%) in the triple-combination group versus 50% in the hydroquinone group were satisfied or very satisfied (trial authors report  $P = 0.005$ ).

The ninth RCT [45] was a comparison between triple-combination cream (TCC) and nonablative 1550 nm fractional laser therapy and is reported in the laser therapy section.

The tenth RCT [46] evaluated the safety and efficacy of serial GA peels in combination with topical AZA 20% and adapalene 0.1% gel versus treatment with AZA 20% and adapalene 0.1% only on 28 patients (one man) with epidermal melasma (by Wood's lamp examination) for a treatment period of 20 weeks. The chemical peel group (16 patients) received eight GA peels (Glycolic Acid Peel Solution, Neostrate) every other week for 3–5 min with a gradually increasing concentration of 20–35–50–70%, combined with AZA 20% cream b.d. (Skinoren cream, Schering Pharmaceuticals, Turkey) and adapalene 0.1% gel o.d. (Differingel, Liba Pharmaceuticals, Kavacik, Istanbul, Turkey) for 20 weeks. The control group (12 patients) used only AZA cream and adapalene gel without chemical peeling. The MASI score was obtained at baseline and every 4 weeks. A significant decrease of the MASI score was found in both groups, with an 83.08% ( $P < 0.001$ ) change in the chemical peel group and a 69.34% ( $P < 0.005$ ) decrease in the control group. When comparing the two treatments, a significant difference was found in favor



of the peel group at week 12 ( $P = 0.013$ ), 16 ( $P = 0.035$ ), and 20 ( $P = 0.0048$ ).

The eleventh RCT [47], an open-label trial on 120 patients from four centers in Brazil compared the effect of a TCC (hydroquinone 4%, tretinoin 0.05%, flucinolone acetonide 0.01%) daily with hydroquinone 4% (HQ: Claripel™ Stiefel Laboratories INC., Miami FL) b.d., used for 8 weeks. Both groups applied SPF 30 sunscreen at least once a day. Every 2 weeks the investigators evaluated melasma severity using a 0–3 scoring system (0: lesion very similar to the surrounding skin; 3: markedly darker) and overall improvement using a 5 to –1 score (5: 100% clearance; –1: worsening). Primary success was defined as score 0 at week 8; secondary success was an improvement score 3–5 ( $>75\%$  improvement). Patients performed an end-of-treatment overall evaluation using a scale 4 (excellent) to 1 (poor). In the TCC group, melasma score was significantly lower at weeks 4, 6, and 8 ( $P < 0.003$ ). Primary success was achieved for 35% of the TCC group versus 5.1% of the HQ group ( $P < 0.0001$ ); secondary success was achieved for 73% of TCC and 49% in HQ. Treatment rated as excellent was 50% for TCC and 34% for HQ.

### Drawbacks

The reasons for withdrawals in the first RCT [20] are not clear. Numbers were similar in the two groups: six of 25 (24%) in the AZA, tretinoin, and sunscreen group versus seven of 25 (28%) in the AZA and sunscreen group (RR, 0.9; 95% CI, 0.3–2.2).

In the second RCT [39] the AZA group experienced significantly more burning and peeling. There were two withdrawals in the AZA group and four in the hydroquinone group. However, these were described as not being due to side effects of the preparations.

All participants in the third RCT, comparing a combination of hydroquinone and GA followed by sunblock with or without 2% kojic acid [40], complained of redness, stinging, and mild exfoliation on both sides of the face. These adverse events settled by the third week of the study. No further details were provided. Three women withdrew from the study because of adverse effects on both sides of the face, and were replaced by three other women.

In the fourth RCT comparing alpha hydroxyl acid, polypeptide ascorbate complex, and titanium oxide photoprotector with a preparation containing titanium oxide photoprotector [41], one woman withdrew after 28 days because of depigmentation. However, no detail is provided on whether this happened on the intervention or control cheek. A second participant was excluded when it became apparent that she did not have melasma. In the active treatment group, a higher frequency of erythema and a burning sensation was reported, and this persisted throughout the follow-up period. However, no further details are provided.

In the fifth RCT [42], both treatments were described as being well tolerated, although all participants had some degree of skin irritation. Kojic acid gel was found to be a stronger irritant. No further details are provided.

In the sixth RCT, all the side effects reported were either mild or moderate and included burning, itching, dryness, redness, and peeling. No serious side effects were seen [43].

In the seventh RCT [16], a total of 387 of the 642 patients suffered side effects such as erythema, desquamation, burning, dryness, and pruritus, but these were considered to have been related to the study drugs in only 16 of the patients. In the results section, percentages are used instead of numbers of patients, and no description of –outs is given. Only one patient receiving HQ+FA suffered from skin atrophy. The authors suggest a protective effect of retinoids as a possible mechanism.

In the eighth RCT [44], adverse events were significantly more frequent in the triple combination groups compared with hydroquinone (RR, 3.55; 95% CI, 2.23–5.65). The most commonly reported side effects were erythema, irritation, and discomfort of the skin, though this was stated to be mild in intensity.

In the tenth RCT [46], mild burning and itching were reported with the AZA cream which resolved within a few weeks. No side effect was noted with the adapalene cream. Three patients experienced moderate to severe epidermolysis after the GA peel, requiring treatment with topical bethamethason valerate 0.1% cream for 7 days.

In the eleventh study [47], one drop-out was reported from the HQ arm due to a non-drug-related adverse event. Erythema, burning sensation, and desquamation were reported as the most frequent side effects in both groups, with no significant difference between the two arms. At week 8, facial telangiectasia occurred in 15% of the TCC group and in 9% of the HQ group (no  $P$  value provided). Systemic side effects were also reported in both groups, the most frequent being headaches (TCC: 11; HQ: 9).

### Comments

Methodological limitations, such as high withdrawal rate, compromise the validity of the results in the first RCT comparing AZA, tretinoin, and sunscreen with AZA and sunscreen [20].

In the second RCT, comparing AZA cream, GA, and sunscreen with hydroquinone and sunscreen, it was not possible to determine if the response varied between people with melasma and people with other hyperpigmentation conditions [39]. It is therefore difficult to draw valid conclusions.

The third RCT, comparing a gel containing kojic acid, hydroquinone, and 10% GA followed by titanium dioxide sunblock with a gel containing hydroquinone and GA followed by titanium dioxide sunblock had a small sample size which may have been insufficient to rule out an effect [40]. Other limitations include the lack of detail on allocation concealment and the lack of objective measures of improvement.

The fourth RCT [41] did not provide details on the melasma type. Melasma type has been associated with treatment response. The study does not give details of the kind of alpha hydroxyacid used and lacks details of demographic data.

The fifth RCT does not allow one to look at variables, but gives percentage improvements and  $P$  values. It concludes that the addition of 2% kojic acid gel to GA is as efficacious as 2% hydroquinone [42]. The addition of 2% kojic acid to a gel containing 10% GA and 2% hydroquinone further improves melasma. No additional side effects were reported on the kojic acid side [40].

The sixth RCT [43] found that the improvement seen with the compound cream on the patient assessed results was much less marked compared with physician subjective MASI reduction or mexameter results. No explanation is provided for this. Additionally, four women were lost to follow-up and it is unclear which group this is from.

The seventh RCT [16] has some methodological drawbacks. The publication combines the results of two separate studies, and the authors do not provide any details of these studies. The randomization methods are not clear. The results section only provides percentages, and there is no mention of drop-outs.

The eighth RCT [44] had patient and physician assessments as well as quality-of-life scores. Intention-to-treat analyses was performed. However, there were no objective measures of improvement.



In the tenth the study small sample size provides only weak evidence to support the superior effect of GA peels in combination with AZA and adapalene [46]. The study does not give details of variables, but lists only *P* values and mean value of improvement. Side effects were only mentioned with the use of AZA, although it was applied in combination with adapalene [46].

In the eleventh RCT [47] the type of melasma is unknown. No objective data analysis was performed, but a subjective scaling system was used to measure outcomes.

### Key messages

A variety of combination creams was used. Some studies had significant methodological flaws that compromised the validity of the results, including small sample sizes or lack of objective measures. There was limited evidence for each cream as each formulation was unique and studied in one RCT each except the TCC (RA+HQ+FA) in three RCTs. The TCC was more effective than any of the agents in dual combination. The TCC was also shown in another two RCTs to be more effective than 4% hydroquinone alone. A different formulation of the triple-combination cream with a higher percentage of hydroquinone (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1%) was used in another RCT and found to be equally effective to laser therapy with a nonablative fractional laser (reported below).

### Implications for clinical practice/categorization

TCC may be effective.

### Laser therapies

#### Efficacy

We found one systematic review [21] and seven RCTs.

The first RCT [48] included eight dark-skinned people (skin phototypes IV–VI) with dermal melasma diagnosed using a Wood's lamp. The article does not provide any details of the participants' demographic data. All of the participants received a 14-day course of 0.05% tretinoin cream, 4% hydroquinone cream, and 1% hydrocortisone cream, applied twice daily. They were asked to use a sunblock of SPF 15 or higher. The participants had a 1 cm<sup>2</sup> area of the face exposed to one pass of the 950µs pulsed carbon dioxide laser, with a computerized pattern generation set at 300 mJ/cm<sup>2</sup>. The intervention group received, in addition to the above, another pass with a Q-switched alexandrite pigment dye laser at a dose of 6 J/cm<sup>2</sup>. The treated area was evaluated after 6 months. Normal skin was found in three participants in the intervention group and one in the control group. However, the sample size is too small for valid conclusions to be drawn, and there were confounding factors such as the use of different sunblock preparations.

The second RCT [49] was in Taiwan on 33 participants with mixed-type melasma previously unresponsive to hydroquinone. Participants were randomized to receive either 4% hydroquinone cream or four sessions of intense pulsed light and 4% hydroquinone cream over 16 weeks. Intense pulsed light is a broad-spectrum light with wavelengths ranging from 400 to 1200 nm that penetrates the skin's surface and targets specific elements in the skin, such as melanin. There was a co-intervention of a broad-spectrum sunscreen. In the hydroquinone-only group, 64% of the participants were slightly satisfied and 36% were unsatisfied. In the pulsed light and hydroquinone group a higher proportion were slightly satisfied, 76.5%, and 23.5% were unsatisfied. Improvement was also assessed objectively, and a greater reduction in the melanin score was seen in the hydroquinone and intense pulsed light group.

The third RCT [45] was on 20 female patients (skin types II–V) with moderate to severe melasma. Patients were randomly assigned to once-daily triple-combination cream (hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1%) for 8 weeks or laser therapy. Laser therapy was four sessions of nonablative 1550 nm fractional (Fraxel Re:store laser, Reliant technologies Inc, Mountain View, CA) laser treatment at 2-week intervals. Patients were instructed to use sunscreen (SPF >50) every 3 h when outside. Participants were assessed objectively with melanin index readings and subjectively with MASI and physician global assessment scores. There was also self-assessment (patient global assessment). At 3-week follow-up there was no significant difference in the MASI or melanin index between the groups. There was also no significant difference from baseline or between the groups on the patient global assessment. There was, however, a significant improvement in both groups on the physician global assessment (*P* < 0.001). Mean treatment satisfaction was significantly higher in the laser group (8.3 vs 5.3; *P* < 0.05). There was recurrence in both groups at 3 months, and at 6 months the follow-up scores on the physician global assessment returned to baseline.

The fourth RCT [35] has been included in the acid peels section. Participants were treated with the pigment-specific Q-1064 nm and one half of the face randomly assigned to be treated with GA peels.

The fifth RCT [50] was a single-blind split-face study on 17 patients (phototypes II–IV) comparing triple-combination cream with TCC and pulse dye laser (PDL – Vbeam; Candela Corporation, Wayland, MA). No demographic data were included. Outcomes were assessed by a single blinded investigator. The MASI score on digital photographs was used. Tolerance and satisfaction were graded by the patients on a VAS. The rationale for using a PDL was to treat vascularization and solar elastosis associated with melasma and possible reduction in recurrence. All patients were recruited in winter, and photographs were taken after treatment and after summer, at least 2 months after the last treatment. There was no difference in response for skin type IV patients for initial improvement and recurrence between the two sides of the face. There was significant improvement in melasma in all treatment groups, but the recurrence of melasma was significantly less in the TCC and PDL-treated side of the face compared with the TCC-only side of the face (*P* < 0.01 vs *P* = 0.13). Half of the patients reported mild irritation with TCC. Three patients with skin type IV developed postinflammatory hyperpigmentation. The authors felt this was due to PDL targeting melanin and suggest not to use this in patients with skin type IV.

The sixth RCT [51], from Korean authors, compared the efficacy and adverse effects of a 1064 nm Q-switched Nd:YAG laser (Spectra VRMIII, Lutronic Corp., Seoul, Korea) when used before or after TCC hydroquinone 4%, tretinoin 0.05%, and fluocinolon acetonide 0.01% (Tri-luma® Galderma Lab LP). The study used “laser toning” treatment with top-hat beam mode, short pulse width, high peak power, and low fluence. Over a period of 16 weeks 13 patients (skin types III, IV) with symmetrical distribution of melasma applied TCC once daily, side effect permitting, on one side of the face for 8 weeks, then were treated weekly for 8 weeks with a Q-switched Nd:YAG laser using a collimation hand piece with a 1064 nm wavelength, a 7 mm spot size, a fluence of 1.6–2.0 J/cm<sup>2</sup> and two passes per session. On the other side of the face the treatment was performed in a reversed order, using laser first than applying TCC. After laser treatment, prednicarbate 0.1% ointment (Dermatop ointment Dermik Laboratories, Bridgewater, NJ) was

used to reduce inflammation. All patients avoided sun exposure and used sunscreen with SPF 50 and UVA protection. Efficacy was assessed weekly using clinical images, MASI scores, spectrophotometry measuring brightness, and overall color differences. Patient self-evaluation was also measured at the end of week 16 and 11 months after treatment. In both groups the overall reduction of the MASI score was significant ( $P < 0.05$ ); however, overall improvement measured by spectrophotometry showed significant improvement only in brightness achieved with TCC followed by laser treatment. In all other groups, spectrophotometry failed to prove significant improvement. Comparing the two methods, laser treatment was more effective than TCC in reduction of MASI ( $P < 0.05$ ), but the overall improvement between the two groups was not significant ( $P > 0.05$ ). Again, spectrophotometry showed no statistically significant improvement between the two methods during or at the end of the treatment period. On patient subjective assessment, laser treatment with pretreatment TCC was significantly more effective than posttreatment TCC.

The seventh RCT [52], from Amsterdam, compared triple treatment therapy (TTT – hydroquinone 5%, tretinoin 0.05%, triamcinolone acetonide 0.1% cream) with nonablative 1550 nm fractional laser therapy (Fraxel Re:store laser, Solta Medical, Inc., Hayward, CA). This was a split-face study involving 29 patients aged 18 or over with skin types 2–4. Patients were followed up for 6 months after the last treatment. Improvement of melasma was assessed by patient's global assessment, patient's satisfaction, physician's global assessment, melanin index, and lightness ( $L$ -value) at 3 weeks, and at 3 and 6 months after the last treatment. This study showed significant worsening of pigmentation on the side treated with lasers ( $P < 0.001$ ). Nine patients (31%) developed postinflammatory hyperpigmentation.

### Drawbacks

In the first RCT [48], two participants in the control group suffered peripheral hyperpigmentation.

In the second RCT [49] there were three drop-outs: two in the control group due to poor compliance and one in the intense light group due to relocation. Side effects in the intense light group consisted of erythema, pain, and microcrust formation. Two patients in this group also suffered transient postinflammatory hyperpigmentation.

In the third RCT [45] the participants in the laser group had erythema (75%), burning (58%), and moderate to severe facial edema (40%). In the triple-combination group, patients reported scaling (55%), erythema (25%), and burning (20%).

In the fifth RCT [50] the authors recognize that the split-face design of the trial was not ideal as hyperpigmentation in melasma is usually asymmetrical. The follow-up period in this study is very short, as melasma can recur sometimes years after treatment. The authors have not provided us with data on individual patients or the length of time between the last treatment and final follow-up.

In the sixth study [51], 23% of patients showed worsening of melasma after TCC treatment; no worsening was reported with laser treatment. Results were maintained with laser in the majority of group A, but it was not achieved in group B. Other side effects reported for TCC were irritation, which resolved after extending intervals between applications (four patients). Only mild pain and erythema were reported after laser treatment.

The seventh study [52] shows significant side effects with nonablative 1550 nm fractional laser therapy and worsening of pigmentation.

### Comment

The first RCT [48] is of particular interest, as it is one of the only trials on dermal melasma that is probably more recalcitrant. The small sample size, however, does not allow firm conclusions to be drawn. Properly designed RCTs are needed to determine the effect of laser therapies in dermal melasma.

In the second RCT [49], the frequency of hydroquinone application in either group is unclear. The rationale for hydroquinone in the control arm where participants have been shown to be unresponsive is also unclear. Additionally, the difference between the two groups, although statistically significant after 16 weeks ( $P < 0.05$ ), was not significant at 36 weeks, indicating a requirement for further treatment courses.

In the third RCT [45], no significant difference was found between laser and TCC by the patients and on the measures of MASI and melanin index. The sample size had been powered to detect a difference in the physician global assessment and may have been too small to detect differences in other outcomes.

The fifth RCT [50] does show some response to treatment with PDL, which is a treatment of vascular lesions. The authors hypothesize that this is due to a possible role of vascularization in the development of melasma.

The findings of the sixth study [51] were limited by small patient number. Long-term outcome measures were only assessed by patient self-evaluation, and no statistical analysis was performed.

In the seventh study [52] the authors argue that the reason for the observed hyperpigmentation was the higher setting used 15 mJ/microbeam.

### Key messages

We found insufficient evidence to evaluate the effect of laser therapies in the treatment of melasma. The second study shows some short-term results with the use of an intense pulse light. Repigmentation 8 weeks after the last course of intense light treatment was noted despite continuous use of hydroquinone and broad-spectrum sunscreen. In one RCT, nonfractional ablative laser therapy (1550 nm) was not found to be significantly different to TCC. In both groups, melasma recurred to baseline at 6-month follow-up. Nonfractional laser therapy may have a short-term benefit. The fifth study shows PDL may help in reducing recurrences of melasma, although the follow-up period was very short in this study. In the sixth study, no significant difference was found when comparing the combination treatment with Nd:YAG laser before or after TCC application. The seventh RCT shows significant problems with the use of nonablative 1550 nm fractional laser therapy and the authors concluded against its use in the treatment of melasma using 15 mJ/microbeam. This study was conducted in springtime, which may explain the higher rate of postinflammatory hyperpigmentation.

### Implications for clinical practice/categorization

Unknown effectiveness.

### Oral and topical vitamins

#### Efficacy

We found one systematic review [21] and three RCTs. The first RCT [27], from Japan, included 176 women and two men over a period of 3 months. Melasma was present in 136 of the patients (76%) and pigmented contact dermatitis in 42 (24%). Specific results for melasma were available from the study report. The RCT compared

oral vitamin E (50 patients), vitamin C (45 patients), and a combination of vitamins E and C (41 patients). After 12 weeks, the physician-rated color difference and photographic findings were used to assess changes. Using color photographs, an improvement was noticed in 69% of those receiving a combination therapy of vitamins E and C, 60% of those receiving vitamin E, and 50% of those receiving vitamin C. These differences did not reach statistical significance. In the objective clinical improvement evaluation, 72% of the participants in the combined-therapy group showed improvement, in comparison with 63% in the vitamin E group and 44% in the vitamin C group. The difference between the combined-therapy and vitamin C groups reached statistical significance ( $P < 0.05$ ).

The second study [53] was a split-face double-blind RCT conducted in Seoul, South Korea, on 29 women (aged 24–49) with melasma. It compared iontophoresis with a topical compound containing ascorbic acid, magnesium-L-ascorbyl-2-phosphate, against distilled-water iontophoresis. This was a split-face trial (with the left- and right-side agents selected randomly), and the patients were treated twice weekly for 12 weeks, with concomitant use of a sunscreen twice a day on both sides of the face. Interestingly, subjective assessment by patients did not show any differences between the two sides, but measurement of the *L* value (measured by a colorimeter) showed a significant difference in favor of ascorbic acid: from  $L = 4.60$  to  $2.78$  ( $P = 0.002$ ), in comparison with control side from  $4.45$  to  $3.87$  ( $P = 0.142$ ).

The third RCT [54], a randomized, double-blind placebo-controlled study, evaluated the effect of oral procyanidin+vitamins A, C, and E among 60 Filipino patients with epidermal melasma. Procyanidin is the main active constituent of French maritime pine (*Pinus pinaster*) with anti-inflammatory and antioxidant properties. Sixty subjects (skin types III–IV) with epidermal melasma were randomized to take either test drug (24 mg procyanidin, 6 mg  $\beta$ -carotene, 60 mg ascorbic acid, 15 IU D- $\alpha$ -tocopherol acetate) or placebo (containing starch) b.d. for 8 weeks. An SPF 24 sunscreen was applied daily. The degree of pigmentation was measured with a mexameter and the MASI score was obtained at baseline and at weeks 4 and 8. By mexametry, average melanin index decreased significantly in the treated group ( $P < 0.0001$ ), while no significant changes were measured in the placebo group. The MASI score improved significantly for both with a between-groups change of  $P < 0.0001$ . Subjective measures like physicians' global assessment score showed moderate to obvious results, but the patients' global assessment score showed a wide range from slight to moderate improvement.

### Drawbacks

There were 10 withdrawals in the Japanese RCT [27]. One participant withdrew because of side effects, while 51 failed to complete the 12-week follow-up. Five people in the group receiving vitamins E and C suffered side effects: two had acne, one had xerosis, one had a mild stomach upset, and one developed metrorrhagia. Eight people in the vitamin E group complained of side effects: four had acne, one had a stomach upset, one had excessive perspiration, and two developed menstrual abnormalities. Side effects were also reported by participants receiving vitamin C: four suffered acne, two hot flushes, one had a stomach upset, and one developed seborrheic dermatitis.

The second RCT [53] reported a mild sense of electric shock in 21% patients, itching and erythema in 7%, and burning sensation and dryness in 3%.

In the third study [54] there were three patients who failed to appear on follow-up and one subject dropped out due to developing a metallic taste. No other side effect was reported.

### Comments

The Japanese study did not have a placebo group, and all of the groups improved. Improvement was better in patients receiving preparations containing vitamin E. A placebo-controlled study is needed to determine the effect of these compounds. Thirty-one people suffered side effects, although it is not clear whether this refers to people with chloasma or whether it included people with other pigmentary disorders. In the second RCT, although the objective evaluation using the colorimeter found a significant difference with more improvement on the vitamin-C-treated side, the participants' self-assessment detected no difference between treatments. The third study reported no standard deviation (SD) values of mexametry, and the MASI score and patient's own assessment showed a wide range of outcomes. It was a study with small patient numbers and lacked long-term follow-up data.

### Key messages

We found limited evidence that a combination of vitamins C and E is better than vitamin C alone. We found no evidence in favor of vitamin C iontophoresis versus placebo. Procyanidin in combination with vitamins A, E, and D might be effective in the short term, but further studies are needed in the future to confirm benefits.

### Implications for clinical practice/categorization

Unknown effectiveness.

### Less conventional therapies

#### Efficacy

We found one systematic review [21], which concluded some efficacy of unconventional therapies. We found six RCTs. The first RCT [55] was in Brazil. It was a double-blind, RCT comparing 4% hydroquinone and a skin-whitening complex developed in France. The cream contained: (1) extract of uva ursi, which provokes chemical discoloration of melanin and competes with the tyrosinase enzyme; (2) biofermented *Aspergillus*, which chelates copper ions, which are essential for tyrosinase enzyme activity; (3) grapefruit extract, rich in citric and malic acids, with an exfoliative action; (4) rice extract, rich in oligosaccharides, with a hydrating function. The study was conducted in 30 women aged 38–56, with Fitzpatrick skin types III–V, and with no previous treatments over a period of at least 6 months. The patients were randomly assigned to receive either 4% hydroquinone or skin-whitening complex on one side and a placebo cream on the other side. The treatment was carried out for 3 months, with the addition of a sunblock during the treatment period. Photographs were taken before and after treatment and clinical evaluation was performed by two independent observers and by the patients themselves. The two groups were evaluated separately. Group 1 (hydroquinone vs placebo) had an improvement of 76.9% and group 2 (skin-whitening complex vs placebo) showed an improvement of 66.7%; however, the difference was not statistically significant on Fisher's test ( $P = 0.673$ ).

The second RCT [56] was a split-face trial on 28 women with mixed melasma in the Philippines. Participants applied Gigawhite solution or placebo to either the right or left side of the face twice daily for 12 weeks. Gigawhite is a complex of botanical origin containing mallow, peppermint leaf, *Primula veris*, *Alchemilla vulgaris*,



*Melissa officinalis* leaf extract, and *Achillea millefolium* extract. There was also a co-intervention of SPF 60 sunscreen. Three participants had a greater than 90% improvement, 15 had a greater than 50% improvement, and seven participants a greater than 25% improvement. It is unclear if this was compared with baseline or if compared with the placebo side. The decrease in MASI was not significantly different for the two sides, although there was greater decrease on the Gigawhite-treated side. There was a decrease in MASI by 18.5% (mean) on the Gigawhite side compared with 13.5% (mean) on the placebo side. Although no significant differences were noted on subjective measures, the colorimeter analysis found a significant difference with improvement of 6.9% (mean) in luminance on the Gigawhite side compared with 1.03% (mean) on the placebo side at 12 weeks (the trial authors stated  $P = 0.013$ ).

The third RCT [57] was a split-face trial on 32 women with moderate to severe melasma. Participants were randomized to rucinol (4-*n*-butylresorcinol) serum or placebo to the right or left side of the face applied twice daily for 12 weeks. Rucinol is a resorcinol derivative shown to inhibit the activity of both tyrosinase and TRP-1. All participants were provided with an SPF 60 broad-spectrum sunscreen. There was also an optional stage of the study (phase 2) where open treatment of the whole face was carried out using the active product for 3 months during which time participants received rucinol on both sides of the face. A clinical pigmentation score from 0 (no pigmentation) to 10 (brown pigmentation of high intensity) was allocated for different regions of the face (forehead, malar, and chin) and a mean taken. A significantly lower pigmentation score was achieved on the side treated with rucinol ( $P = 0.027$  reported). The mean clinical pigmentation score at baseline in the rucinol group was 7.5 (SD 1.9) and at 12 weeks it was 6.2 (SD 2.3). In the placebo group the score at baseline was 7.5 (SD 1.9) and at 12 weeks was 6.7 (SD 2.1). The small reduction in score seen in the placebo group was attributed to sunscreen use. Colorimetric assessments using the chromameter confirmed that the rucinol-treated side was significantly lighter and less yellow at 12 weeks. When pigmentation scores in phase 2 (at 16, 20 and 24 weeks) were compared with those recorded at the end of 12 weeks, the differences were found to be highly statistically significant ( $P = 0.004$  at 16 weeks) at each visit for the side previously treated with vehicle. For the side treated with rucinol throughout the study, there was also a statistically significant improvement at 16 weeks compared with 12 weeks. The authors concluded that the effect of rucinol was maintained until the end of the study at 24 weeks.

The fourth RCT [58] was conducted in Belgium on 27 women with melasma affecting the forehead for at least 6 months. Participants were randomized to Thiospot intensive, a cosmetic whitening formulation containing ethyl linoleate, thioctic acid, octadecanedioic acid, lactic acid, and ethyl-hexyl-methoxycinnamate, or Eucerin non-whitening skin care, both applied twice daily for 3 months. Thiospot is purported to inhibit the enzyme tyrosinase involved in melanin synthesis. There was a significant difference between the groups. At 3 months the group receiving Thiospot had lighter skin with a lower melanin index measured using a mexameter ( $P < 0.01$ ). The significant improvement in melasma in the Thiospot group was also confirmed on the other objective measurements of video-recorded ultraviolet light reflection, corneometer, as well as the physician's subjective assessment.

The fifth RCT [59] from San Jose, CA, a split-face, randomized, double-blind, placebo-controlled pilot study evaluated the efficacy of a proprietary synthetic oligopeptide (Lumixyl™, Emed, Inc., Westlake Village, CA) with competitive tyrosinase-inhibiting prop-

erties on patients with moderate recalcitrant, epidermal melasma (Wood's light assessment). Five female patients (skin type IV) with Hispanic or Asian descent who just failed a 6-month twice daily treatment with Tri-Luma® were enrolled and treated with 0.01% Lumixyl and vehicle alone on either side of the face, twice daily over a period of 16 weeks. The investigators rated improvement of melasma on a 10-point scale by using digital photographs at weeks 12 and 16. Additionally, at week 16, physicians and patients graded overall facial appearance using a four-point global assessment scale and patients' satisfaction with the treatment were also evaluated. Both patients' and physicians' assessments showed >40% improvement in melasma at week 12 and >50% at 16 weeks on the oligopeptide-treated site versus 4% improvement on the placebo site. Global assessment also demonstrated >70% improvement in overall appearance of the facial skin on the site treated with the active ingredient versus 15% improvement on the placebo-treated site. Patients were either very satisfied or extremely satisfied on the oligopeptide-treated site compared with mild satisfaction and not satisfied at all on the placebo site.

The sixth RCT [60], from Brazil, compared a combination of plant extract belides, emblica, and licorice 7% (group A) with hydroquinone 2% (group B) in the treatment of melasma. This study involved 56 females, 18–60 years of age, phototypes I–IV, with epidermal or mixed melasma. Before entering the study they had to use an SPF 50 sun block for 60 days. They were randomized into two groups; six patients did not complete the study. Evaluations were done 15 days apart for 60 days by the patients, physicians, and with digital photography (VisiaR, Canfield Imaging System – Fairfield, EUA). Both groups showed significant improvement in lightening of melasma by physician-reported evaluation (group A: 78.3%; group B: 88.9%) and patients' self-evaluation (group A: 91.3%; group B: 92.6%); these results were statistically significant ( $P < 0.001$ ), with no differences between groups ( $P > 0.05$ ). Digital photography results also showed similar results.

### Drawbacks

In the first study [55], there were no side effects in the extract of uva ursi skin-whitening group, in comparison with the 4% hydroquinone group, in which 25% patients suffered minor side effects.

In the second RCT [56] there were no adverse effects due to Gigawhite or placebo.

In the third RCT [57] there were four withdrawals (12.5%), and 28 participants completed the 12-week study. No reasons for withdrawal were given. There were 12 adverse events reported, the majority of which were mild. The authors felt only one was related to the study product, a small depigmented spot due to placebo. It is unclear if the numbers of adverse events include the extended phase of the study.

In the fourth RCT [58], no adverse events were mentioned in the text.

In the fifth study [59], the oligopeptide was well tolerated with no side effects.

In the sixth RCT [60], two patients in group A and seven in group B suffered mild side effects. There were six withdrawals, which were due to noncompliance with the study protocol.

### Comments

The first RCT [55] did not show any significant improvement in melasma with the use of the skin-whitening complex compared with hydroquinone 4%.



In the trial [56] of a botanical extract, Gigawhite 5%, no significant difference to placebo was noted on subjective assessment by the physicians, though colorimeter analysis showed that the side treated with Gigawhite was significantly lighter. The participants' self-assessment was also poorly reported. It is unclear if the percentage improvement recorded was compared with baseline or if compared with the placebo side. In addition, it was stated that two participants had no improvement and one had worsening of melasma; these three appear to have been unaccounted for in the patient self-assessment above.

In the third RCT [57], although a reduction in the clinical pigmentation score was also seen at the earlier assessment of 8 weeks, the score was not significantly different from baseline, and rucinol may have a slower onset of action.

The fourth RCT [58] had unusual inclusion criteria of forehead melasma. It is unclear if participants were excluded if they had melasma elsewhere (e.g., cheeks or chin). No explanation is given as to why the authors limited inclusion to forehead melasma. There was no description of the type of melasma and no baseline characteristics for each group provided.

There were only five patients enrolled in the fifth study [59]. No objective assessment was carried out and no long-term follow-up was arranged.

In the sixth RCT [60], methods of randomization were not discussed. The evaluators were not blinded in this study.

### **Key messages**

Each agent was trialed in one RCT, each providing limited evidence. We found no evidence in favor of skin-whitening complex extract of uva ursi versus hydroquinone 4%. Although on colorimeter analysis there was significantly more improvement in melasma on the Gigawhite-treated side, the clinical improvement may have only been minimal as the physicians in the study did not note a significant difference to placebo. Rucinol may be effective, though it may have a slower onset of action. Thiospot was more effective than placebo at lightening melasma, though this was in a small study with some flaws. The oligopeptide Lumixyl, a competitive inhibitor of tyrosinase, might be a candidate for further clinical evaluation, but at the moment there is no evidence to support its effectiveness in the treatment of melasma. The sixth RCT shows similar efficacy of plant extracts belides, emblica and licorice 7% compared with 2% hydroquinone. These should be further evaluated by a larger double-blinded study.

### **Implications for clinical practice/categorization**

Unknown effectiveness.

## **How effective are therapeutic interventions in men?**

### **Case scenario 55.4**

A 40-year-old Latin-American man living in California has had melasma for 3 months. It appeared after a beach holiday. He is not on any regular medication, but has a family history of melasma.

### **Efficacy**

We identified no studies assessing the effects of therapeutic interventions exclusively in men. Although several RCTs included a few men, none of them carried out a subgroup analysis, and none would have had sufficient power to identify any clinically relevant differences.

### **Comment**

On the basis of expert opinion, the same treatments used in non-pregnant women may be considered appropriate in men with melasma.

### **Key messages**

We found no evidence specifically evaluating the effects of treatment in men.

### **Implications for clinical practice/categorization**

Unknown effectiveness.

## **Implications of the available evidence**

### **For consumers (the public)**

Current opinion, based on known risk factors, suggests that measures preventing exposure to sunlight may reduce the risk of the development and recurrence of melasma. From the available trial evidence, therapies likely to be beneficial are AZA, hydroquinone, and TCC (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%).

### **For clinical practice (health-care providers)**

From the available evidence, a treatment likely to benefit patients with melasma is 2–4% hydroquinone with sunscreens, and TCC. The use of hydroquinone for melasma has been limited recently, following several case reports of it causing exogenous ochronosis. However, there were no reports of this side effect in any studies with follow-up periods of up to 24 months. TCC (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) was more effective than any of the agents in dual combination and also was found to be more effective than 4% hydroquinone alone. A recent comprehensive review by Sheth and Pandya [61] also suggests a combination of a retinoid, hydroquinone, and a topical steroid to be used as a first-line treatment for melasma.

We did not find convincing evidence for the effectiveness of AZA, topical retinoids, topical corticosteroids, GA, oral vitamins E or C, lasers, or combined therapies.

### **For research (research agencies and researchers)**

We found inconclusive evidence of the effectiveness of topical AZA, steroids, topical retinoids, GA, vitamin C, and laser therapy. These are commonly used therapies for melasma in clinical practice and would require further RCTs to validate their use. Lasers offer a potential advantage over conventional therapies, as the time to clearance can be much reduced. We found only a few studies that looked at patient-based outcomes. Most studies excluded patients with mixed or dermal-type melasma or patients with known risk factors (e.g., recent delivery, oral contraceptive or hormone replacement therapies). Future studies should specify more clearly what type of melasma is being studied, and if participants with a variety of epidermal and dermal patterns are included, then an appropriate subgroup analysis or interaction test should be performed to test the hypothesis that dermal patterns are less responsive to therapy. Future studies need to be much larger, prospectively registered, and reported properly following the latest revision of CONSORT [62].

## Key points

- No clear evidence supports preventive interventions in high-risk populations. Current opinion, on the basis of the known risk factors, suggests that preventing exposure to sources of ultraviolet light, such as sunlight, may reduce the risk of developing melasma.
- No clear evidence supports any therapeutic intervention in pregnant or breastfeeding women. Current opinion suggests that such women with melasma may benefit from using broad-spectrum sunscreens and avoiding exposure to ultraviolet light, such as sunlight.
- Limited evidence from a single RCT evaluating the effect of therapeutic sunscreens shows that, during the 3-month study period, the majority of women using hydroquinone had improvement, regardless of the addition of sunscreen to their treatment. The study did not describe whether women used other strategies to avoid sunlight.
- Evidence is insufficient to support the use of topical steroids in melasma. There is controversy over the use of topical steroids in this condition. There is limited evidence from one RCT of a quicker response when topical steroids are used sequentially with AZA.
- An effect of topical retinoids on melasma has not been shown, but the available studies found that side effects were common.
- In a small trial, AZA was found to be superior to 2% hydroquinone in achieving improvement in people with melasma. We found no solid evidence comparing AZA with placebo. AZA was associated with a higher incidence of side effects.
- Limited evidence from one RCT suggests that hydroquinone plus sunscreen was better than sunscreen and placebo.
- The evidence is insufficient to assess the effects of GA.
- TCC (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) was more effective than any of the agents in dual combination and also was found to be more effective than 4% hydroquinone alone. Overall, we found no good evidence of the effects of other combined therapies in comparison with a placebo or other preparations. The studies had methodological flaws, including small sample sizes, which compromised the validity of results.
- We found insufficient evidence to evaluate the effect of laser therapies in the treatment of melasma. One nonrandomized study showed faster improvement with intense pulsed-light therapy. Postinflammatory hyperpigmentation can be a significant side effect of both PDL and Nd:YAG lasers, especially in patients with skin type IV or above.
- We found insufficient evidence that a combination of oral vitamins C and E is better than oral vitamin C alone. We found no evidence of the effects of these therapies in comparison with placebo.
- We found insufficient evidence for the efficacy of a skin-whitening cream containing extract of uva ursi, biofermented *Aspergillus*, grapefruit extract, oligopeptide Lumixyl, and rice extract in comparison with hydroquinone 4%. In a single-blinded study, plant extracts besides, emblica and licorice 7% showed similar efficacy to 2% hydroquinone. This needs further evaluation with larger double-blinded studies.
- No studies have assessed the effect of treatments specifically in men.

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## SECTION 5 Common ailments with significant cosmetic impact

Berthold Rzany, editor

### CHAPTER 56

## Male and female androgenetic alopecia

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### Background

#### Definition

The term “androgenetic alopecia” (AGA) describes a genetically determined condition leading to permanent loss of hair in men and women with normal levels of androgens. Synonymous terms are male-pattern and female-pattern hair loss. Most men with AGA show a typical pattern of hair loss, often beginning at the temples and in the vertex area [1–3]. In contrast, most women with AGA have a diffuse thinning in the midline of the scalp [4]. In many, but not all, men and women, the hair loss is accompanied by increased shedding of telogen hair, which is a reflection of shortened anagen growth phases [5,6].

#### Prevalence

AGA affects approximately 30% of men under 30 years of age, 50% under 50 years of age, and 70% under 70 years of age [1,7]. In women, the incidence before menopause is 5–10%, rising to 20–30% after the menopause [8].

#### Etiology

Microscopically, AGA is characterized by progressive shrinking of scalp hair follicles [9]. In many patients, AGA is accompanied by an acceleration of the hair growth cycle, as reflected by decrease of anagen and increase of telogen hair in the trichogram [9]. However, some patients have a normal anagen/telogen ratio despite slowly progressive AGA. Whether and when a scalp hair follicle miniaturizes is dependent on two factors: genetics and androgens [10,11]. Several genes responsible for shrinkage of a scalp hair follicle are suspected [11–14], but are not yet all known. Each scalp hair follicle carries individual genetic information that determines whether and when it will develop a sensitivity towards androgens. Once a scalp hair follicle has become sensitive to androgens, it will progressively shrink during the following years. In men, the most important androgen-driving AGA is dihydrotestosterone (DHT). Within the cells of the hair follicle, DHT is derived from its precursor testo-

sterone by two enzymes: the 5- $\alpha$ -reductase types I and II [15]. DHT appears to be less important in women than in men [16]. In general, androgens can be considered potentially harmful and estrogens potentially beneficial for scalp hair growth in women [14].

#### Prognosis

Without treatment, AGA progresses until all hair follicles that have developed a genetically determined sensitivity towards androgens are miniaturized [9]. The extent of AGA depends on the number of hair follicles with genetic sensitivity to androgens. In its maximal expression, all hairs can be lost from the top of the scalp. In both men and women, occipital hair follicles never develop sensitivity to androgens; they are never lost in AGA.

#### Aims of treatment

Treatment of AGA has two major goals. First, it is important to reliably stop further hair loss. The term “hair loss” does not describe telogen effluvium, but refers to permanent visible thinning of scalp hair density due to miniaturization of hair follicles. Second, some men and women benefit so strongly from treatment that they can regrow hair to a certain extent – their hair density can be increased by reenlargement of individual hair follicles.

#### Relevant outcomes

- *Stopping further hair loss:* in a clinical study setting, this has to be documented after intervals of at least 1 year by microscopic methods such as hair counts or increase of hair weight in a representative area of hair loss.
- *Increase of visible hair density:* this has to be documented by standardized scalp hair photography [17].

A change in the anagen/telogen ratio does not reliably assess the efficacy of treatment against further progression of AGA, because not all men and women with AGA have abnormal anagen/telogen ratios. In addition, some patients with long-standing telogen effluvium never develop AGA [18]. The trichogram, therefore, cannot reliably measure the efficacy of treatment against AGA.

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## Methods of literature search

In the PubMed database, different search terms were used for male and female androgenetic alopecia. For male androgenetic alopecia, the search terms were: “((androgenetic and alopecia) or (\*male and pattern and baldness)) and (finasteride or minoxidil).” For female androgenetic alopecia, the search terms were “((female and androgenetic and alopecia) or (female and pattern and baldness)) and (minoxidil or antiandrogen\* or cyproterone acetate or (cyproterone and acetate) or cyproterone acetate or estrogen\* or estradiol).”

## Questions

### Which topical or systemic treatment can stop further hair loss and increase hair density in men?

#### Case scenario 56.1

The patient is a 28-year-old computer specialist with a 3-year history of gradual hair loss starting at the temples and now also involving the top of the scalp (Figure 56.1).

#### Topical minoxidil for men with androgenetic alopecia

##### Efficacy

We found no systematic reviews. Several randomized controlled trials (RCTs) show that minoxidil 2% or 5% solution applied twice daily can increase test-area hair counts and hair weights in men with AGA [19,20].

##### Drawbacks

In approximately 5% of men, minoxidil causes redness and itching of the scalp skin. In most men, this effect appears to be nonspecific irritation by polyethylene glycol or other solvents; in some, however, a specific type IV allergy against minoxidil is possible [21]. Patients sometimes attribute specific systemic effects such as hypotension or an increase in heart rate to minoxidil, but this is implausible, because serum concentrations of minoxidil are very low after twice-daily topical administration. A large 1-year prospective study including more than 10 000 male minoxidil users showed that there are no serious systemic side effects [22].

##### Comment

Minoxidil 5% solution applied twice daily is a safe and effective topical treatment for AGA in men. There are no conclusive data on

how often minoxidil solution can reliably stop hair loss and increase visible regrowth of hair in men. One of the possible mechanisms is improvement of the microcirculation in the dermal papilla [23–25].

#### Implications for clinical practice

Minoxidil 5% solution can stop hair loss in many men, but hair loss resumes when the applications are stopped. There are no systemic side effects.

#### Systemic finasteride for men with androgenetic alopecia

##### Efficacy

We found no systematic reviews. Two-year results from the largest RCT were reported by Kaufman *et al.* [26]. This international multicenter clinical trial of more than 1500 patients demonstrated a significant increase in hair counts in the finasteride treatment group after 1 year. In the second year, there was stabilization of the increased hair count in the finasteride group. Men on placebo had a progressive loss of hair count in the vertex test area. Men who were switched from finasteride to placebo after 1 year lost the hair gained under finasteride. Therefore, as with other medical treatments for AGA, finasteride needs to be taken permanently to show therapeutic benefit. Visible hair density was also documented by a standardized camera device [17]. After 1 and 2 years, the before and after pictures were judged by an expert panel of dermatologists, who were blinded to the treatment modality. After 1 year, 48% of men in the finasteride treatment group had visibly increased hair density in the vertex area, compared with 7% in the placebo group. After 2 years of treatment, 66% of the men in the finasteride group had visibly increased hair density, compared with only 7% in the placebo group [26]. On the basis of the 5-year data [27], hair loss can be stopped in 90% of men taking finasteride, compared with 25% in the placebo group. In addition to stoppage of hair loss, an increase in hair density was seen in 48% of the men in the finasteride group, compared with 6% of men in the placebo group after 5 years of the study.

Other RCTs have demonstrated that finasteride significantly improves the anagen/telogen ratio [28], increases individual hair weight [29], also has positive effects on the frontal hair line [30], is as effective as minoxidil [31], and also works well in men between 40 and 60 years of age [32].

##### Drawbacks

There were no side effects on the liver, kidney, or any other internal organ [26]. Serum hormones were unaffected, with the exception of a desired 70% decline in DHT and a compensatory 10% increase in testosterone. The following sexual side effects were reported for the finasteride and placebo groups, respectively: a decrease in libido of 1.9% versus 1.3%; a decrease in potency of 1.4% versus 0.9%; and a decrease in ejaculate volume of 1.0% versus 0.4%. Although the differences between the finasteride and placebo groups were small and statistically not significant [26], and were not seen in other studies [33], finasteride must be considered capable of causing such effects in some men. A separate study found sperm function parameters to be unaltered by finasteride 1 mg [34].

##### Comment

Finasteride 1 mg is a safe and effective drug for the treatment of AGA in men. Finasteride inhibits the enzyme 5 $\alpha$ -reductase type II, thereby preventing the intracellular conversion of testosterone into its more active metabolite DHT [35]. In men, DHT is essential for



Figure 56.1 Typical male-pattern hair loss in a 28-year-old patient.

the development of AGA, and finasteride decreases DHT by 70%, both in the scalp skin and in serum [36].

### Implications for practice

In 90% of men treated, finasteride 1 mg can stop hair loss (for at least 5 years) while it is being taken. Systemic side effects such as reduction of libido and erectile function are infrequent (1–2%) and often transient.

## Which topical or systemic treatment can stop further hair loss and increase hair density in women?

### Case scenario 56.2

The patient is a 35-year-old teacher with a 5-year history of gradual hair loss starting at the midline of her scalp (Figure 56.2). Her mother also had thin hair; her father was bald.

### Topical minoxidil for women with androgenetic alopecia

#### Efficacy

We found one systematic Cochrane Collaboration review [37]. Several RCTs demonstrate that minoxidil 2% solution applied twice daily can increase test-area hair counts and hair weights in women with AGA [38,39]. Most trials were conducted for at least 1 year. When effective, minoxidil solution increased visible hair density within 6 months. After 6 months, no further increase was to be expected. A large American multicenter study included 308 women with AGA; 256 women completed the trial. In the minoxidil group, the increase of nonvellus hairs was significantly larger than in the placebo group. On the investigators' assessment, more minoxidil-treated women had visible regrowth of hair than in the placebo group [40].

#### Drawbacks

Patients sometimes attribute specific systemic effects such as hypotension or an increase in heart rate to minoxidil, but the very low serum concentrations of minoxidil after twice-daily topical admin-



Figure 56.2 Typical female pattern hair loss in a 35-year-old patient.

istration make this implausible. In addition, a large prospective study showed that there are no serious systemic hypotensive side effects in female minoxidil users [22]. Minoxidil causes redness and itching of the scalp skin in approximately 5% of women. In most women, this effect appears to be nonspecific irritation by polyethylene glycol or other solvents; in some, however, a specific type IV allergy against minoxidil is possible [21]. In women with oriental, dark complexion, hypertrichosis in the face and other parts of the body can occur as a side effect of minoxidil [41]. Hypertrichosis usually subsides after the drug has been stopped. A study by Lucky *et al.* showed similar efficacy rates of 5% and 2% minoxidil solution for female androgenetic alopecia [38]. However, there was an increased occurrence of pruritus, local irritation, and hypertrichosis in the 5% topical minoxidil group. The manufacturer, therefore, prefers the use of 2% minoxidil solution in women.

#### Comment

Minoxidil 2% solution applied twice daily is a safe and effective topical treatment for AGA in some women while it is used. Minoxidil solution can reliably stop hair loss and increase obviously visible regrowth of hair in 10–20% of women.

### Implications for clinical practice

Currently, minoxidil 2% solution is the only effective way of treating AGA in women. There are no systemic side effects.

## Systemic estrogens and/or antiandrogens for women with androgenetic alopecia

#### Efficacy

Because estrogens have many antiandrogenic actions, it is thought that they may have a positive influence on hair growth. Antiandrogens such as cyproterone acetate and chlormadinone acetate directly block the androgen receptor. However, most women with AGA have normal estrogen and androgen levels [42]. Positive effects of estrogens and/or antiandrogens on hair growth are therefore questionable. There are no systematic reviews. One RCT compared the efficacies of the antiandrogen cyproterone acetate, 52 mg daily on days 1–20 of the cycle, with a twice-daily 2% minoxidil application in 66 women with AGA grades Ludwig I (67%), II (31%), and III (2%). The study duration was 1 year, and each treatment group consisted of 33 women. The main outcome was number of strong hairs ( $>40\mu\text{m}$  in diameter) in a test area as detected by the phototrichogram. After 1 year, hair counts in the  $0.32\text{cm}^2$  test area were  $-2.4 \pm 6.2$  in the cyproterone acetate group and  $+6.5 \pm 9.0$  hairs in the minoxidil group [43]. Thus, 2% minoxidil was significantly more effective than cyproterone acetate.

#### Drawbacks

Systemic 17- $\beta$ -estrogens are thought to slightly increase the risk of breast cancer and (particularly in women with coagulation disorders) deep venous thrombosis.

#### Comment

In theory, women using estrogens and/or antiandrogens may benefit from treatment [44]. However, as yet, there is little convincing evidence that estrogens and/or antiandrogens can stop or delay AGA.

### Implications for practice

There are no convincing data showing that systemic estrogens or antiandrogens are effective in women with AGA. We are therefore

reluctant to treat women with AGA with systemic hormones that increase the risk of deep venous thrombosis and fatal embolism.

## Key points

### Men with androgenetic alopecia

- Topical minoxidil 2% or 5% solution applied twice daily to the scalp is effective for many men with AGA, but hair loss resumes when the applications cease. The RCTs reported are too small to establish percentages for successful stoppage of hair loss and frequency of visible regrowth of hair.
- Large RCTs show that systemic therapy with finasteride 1 mg per day can stop further hair loss in 90% and increase visible hair density in 48% of treated men. However, hair loss resumes when treatment is stopped.

### Women with androgenetic alopecia

- Topical minoxidil 2% solution applied twice daily to the scalp is moderately effective for some women with AGA.
- One RCT using modern methods of hair growth evaluation showed that the systemic antiandrogen cyproterone acetate is less effective than 2% minoxidil solution.

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# Alopecia areata

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## Background

### Definition

Alopecia areata is a familial inflammatory disease with an unknown environmental trigger. It is characterized by discrete, well-demarcated, circular areas of nonscarring terminal hair alopecia and its clinical presentation is most often multifocal [1]. Bald areas frequently contain pathognomonic exclamation-mark hairs. It may occur on any hair-bearing area of the body. Severe disease is disfiguring and may produce total loss of scalp hair (alopecia totalis) or universal loss of body hair (alopecia universalis). There may be associated nail changes; however, the skin is normal.

### Incidence/prevalence

The true incidence and prevalence of alopecia areata is unknown. It is estimated that 1.7% of the population will experience an episode of alopecia areata during their lifetime [2]. Alopecia areata accounts for 2% of new dermatological outpatient department attendances in the UK and USA [3]. While alopecia areata can develop at any age, 30–40% of cases appear before 21 years of age and 20–30% after 40 years of age [4]. The condition occurs with equal incidence in both sexes. The percentage of patients with alopecia areata who go on to develop alopecia totalis/universalis is not known, but estimates range from 7 to 30% [5].

### Etiology

Alopecia areata is thought to be an organ-specific autoimmune disease with a complex genetic etiology with polygenic susceptibility and severity loci interacting with environmental factors [6]. The rate of concordance among monozygotic twins is about 55%, and approximately 20% of patients overall have a positive family history [5]. A large number of potential environmental triggers have been evaluated, including emotional stress, pregnancy, and intercurrent infections. However, no definite associations have been identified [7].

### Prognosis

Regrowth from an initial patch occurs within 6 months in 33% of cases, and within 1 year in 50%; however, 33% never recover from the initial episode [8]. Almost every patient will develop further patches if followed for long enough [4].

Adverse prognostic factors include age less than 10 years at time of first episode, ophiasis pattern or total alopecia, poor response to previous treatment, and the presence of associated atopy, nail dystrophy, or Down's syndrome [1]. The duration of alopecia areata prior to treatment is also thought to be an independent prognostic factor [9].

### Diagnostic tests

The diagnosis of alopecia areata is a clinical one. Exclamation-mark hairs in circular bald areas are pathognomonic. Rarely, a biopsy is required to exclude other forms of hair loss. The hallmarks of an active lesion are a dense lymphocytic infiltrate around the anagen hair bulbs and uniform miniaturization of terminal hairs into vellus-like hairs [10]. Telogen hairs are not inflamed, and there are decreased numbers of terminal anagen hairs.

### Aims of treatment

The aim of treatment is to improve the patient's quality of life either by achieving cosmetically acceptable hair regrowth, or by encouraging the patient to live with the hair loss. Unfortunately, the environmental events that trigger episodes of alopecia areata are unknown, and so relapse can be neither predicted nor prevented. Treatment is often unsatisfactory and centers on the provision of emotional support to distressed patients and their families.

### Methods of search

- Clinical evidence search and appraisal (May 2012).
- Supplementary search of Medline from 1966 to 2006.



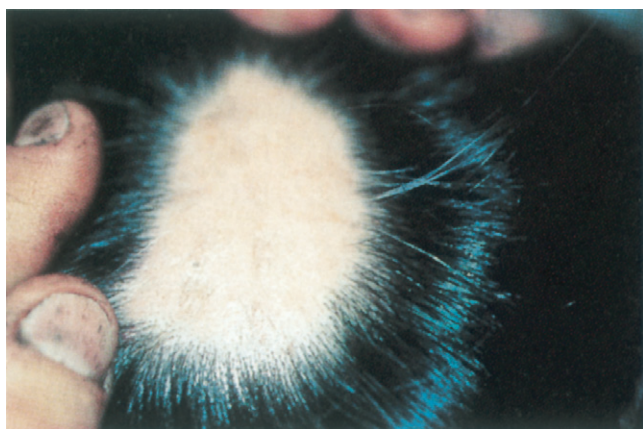


Figure 57.1 Patchy alopecia areata.

- Other references obtained from reference lists in all identified review articles and relevant sections of new editions of multiple-author textbooks of dermatology and hair diseases.
- Cochrane review on interventions for alopecia areata published in 2008 was studied for new content and references.
- A new literature review was carried out on articles published between 2006 and 2012 for this edition.

## Questions

### What are the effects of treatment for patchy alopecia areata?

#### Case scenario 57.1

Sarah is 22 years old and has two patches of alopecia areata over the frontal and parietal scalp that have been present for 8 months (Figure 57.1). At the age of 10, she developed alopecia totalis, with spontaneous regrowth after 9 months. At the age of 14, she developed a solitary patch of alopecia areata, with regrowth after two intralesional injections of triamcinolone acetonide 6 weeks apart.

She has a history of atopy, her mother has idiopathic hypothyroidism, and a great-aunt became totally bald after receiving a telegram notifying her of her husband's death during the Second World War. Sarah's only recent stress was breaking up with her boyfriend of 4 years; however, that occurred after the hair loss had begun.

#### Intralesional corticosteroids

##### Benefits

I found no systematic reviews. One randomized controlled trial (RCT) and one observational comparison study confirm that intra-dermal injections of triamcinolone acetonide, 5 mg/mL with a needle-less injector, produced rapid regrowth of hair in a high proportion of subjects with limited disease within 4–6 weeks.

##### Versus placebo

In a report of 84 patients using normal saline controls, 86% of patients treated with triamcinolone responded, in comparison with only 7% of control patients [11]. Injections of triamcinolone acetonide, 0.1 mL of 5 mg/mL, were given at weekly or two-weekly intervals on three occasions. The number of injections was determined by the size of the area of alopecia, with each injection producing a

tuft of hair approximately 0.5 cm<sup>2</sup>. Ninety-two percent of patients with localized disease showed regrowth at 6 weeks, in comparison with 61% of those with alopecia totalis. This decreased to 71% at 12 weeks for alopecia areata and 28% for patients with alopecia totalis, without further treatment. Topical tretinoin was used as an adjunctive treatment to intralesional corticosteroids in one study [12].

##### Versus each other

In an observational study comparing triamcinolone acetonide and triamcinolone hexacetonide involving 34 areas of alopecia in 11 patients, 64% of the sites injected with triamcinolone acetonide and 97% of the sites injected with triamcinolone hexacetonide regrew [13].

##### Versus topical corticosteroids

One RCT compared intralesional triamcinolone 10 mg/mL every 3 weeks with topical betamethasone valerate 0.1% foam and tacrolimus ointment 0.1%. One hundred and five patients with localized alopecia areata were enrolled, but data were evaluated on only 78 who completed the trial. On completion of the study at 12 weeks, 15/25 patients in the intralesional triamcinolone group, 15/28 in the betamethasone foam group, and 0/25 in the tacrolimus group had achieved >75% hair regrowth in their target patch [14].

##### Harms

Hemorrhage can occur at the puncture site, but can easily be controlled with pressure [11]. No cases of persistent atrophy of skin were seen. The plasma cortisol level was measured in one patient and showed significant suppression, raising the possibility of a systemic effect [11].

##### Comments/implications for clinical practice

Despite the lack of RCTs, intradermal injection of triamcinolone acetonide in concentrations ranging from 2.5 to 10 mg/mL either with a needle or with a needle-less injector is the most widely used first-line treatment for patch alopecia areata. Rapid hair regrowth is achieved in a high proportion of subjects within 4–6 weeks. Dermal atrophy is common, but usually self-limiting. Topical tretinoin is not widely used as an adjunctive treatment, and the reported beneficial effects have not been independently substantiated.

#### Topical immunotherapy

Three agents have been used for topical immunotherapy: dinitrochlorobenzene, diphencyprone, and squaric acid dibutyl ester (SADBE). All are applied topically at weekly intervals following initial sensitization.

##### Benefits

I found one systematic review of published case series on the use of topical immunotherapy with diphencyprone, which concluded that 50–60% of patients achieve a worthwhile response. Patients with limited disease have higher response rates than patients with alopecia totalis/universalis [15].

##### Versus placebo

I found no RCTs. In the largest series reported to date of diphencyprone in the treatment of alopecia areata, 148 consecutive patients were evaluated for unilateral regrowth following unilateral treatment [16]. At 32 months, cosmetically significant regrowth was obtained in 17.4% of those with alopecia totalis/universalis, in

60.3% of those with 75–99% hair loss, in 88.1% of those with 50–74% hair loss, and in 100% of those with 25–49% hair loss. The only other independent predictor of treatment response was the age of onset of alopecia areata, with an older age of onset portending a better prognosis [17]. Relapse after achievement of cosmetically significant regrowth occurred in 62.6% after a 37-month follow-up period and was not prevented by maintenance therapy [17].

#### ***Versus each other***

A controlled trial compared SADBE, diphencyprone, minoxidil, and placebo in patients with patchy alopecia areata involving less than 40% of the scalp [18]. The study included 119 patients and was continued for at least 6 months. No significant differences were found between the different therapies used and placebo.

#### ***Harms***

Dinitrochlorobenzene is mutagenic on the Ames test [19]. A moderately severe allergic contact dermatitis is necessary for success of the therapy [20], which if severe may necessitate temporary suspension of treatment. Tender regional lymphadenopathy is common, but usually mild and self-limiting. Generalized dermatitis is uncommon, but may necessitate permanent cessation. Contact urticaria, vitiligo, and erythema multiforme have been reported [21]. Dinitrophenol, a metabolite of dinitrochlorobenzene, has been reported to cause hepatic and renal changes, convulsive seizures, and hyperthermia [22].

#### ***Comments/implications for clinical practice***

Diphencyprone is not licensed in the USA. Immunotherapy for alopecia areata is only available in specialist treatment centers. I found no RCTs on the use of topical immunotherapy; however, a number of studies have demonstrated unilateral hair regrowth after unilateral treatment. This protocol conforms to the published investigational guidelines for alopecia areata [15]. In almost all case series, patients with limited disease have higher response rates than patients with alopecia totalis/universalis. In contrast to other studies, Shapiro *et al.* [23] found that a long duration of disease did not necessarily preclude a positive response to treatment with diphencyprone. Tosti *et al.* concluded from their work that transferring nonresponder patients with alopecia totalis or universalis to other therapies is generally useless [24].

#### **Topical corticosteroids**

##### ***Benefits***

I found no systematic reviews. There were two well-conducted RCTs with adequate patient numbers to support their use.

##### ***Versus placebo***

In one RCT, which included 70 patients using 0.2% desoximetasone for 12 weeks, there was a trend to more regrowth in the treatment group, but the complete regrowth rates were higher in the placebo group [25]. In the second RCT, 34 patients were enrolled in a randomized, double-blind, right to left, placebo-controlled, 24-week study and scored with the alopecia grading scale in accordance with the alopecia areata investigational guidelines [15]. Patients applied clobetasol foam to half their scalp and placebo foam to the other half. Regrowth was seen in 89% of clobetasol-foam-treated head sites versus 11% in placebo-foam-treated sites. Regrowth was partial, with only three patients achieving 75% regrowth. Two patients developed folliculitis. No significant safety concerns were identified [26]. In an observational study, 0.2% fluocinolone aceto-

nide was used under nighttime occlusion. Of the 47 patients, of whom only 28 were evaluable, 17 (61%) achieved a satisfactory clinical response after 6 months [27]. Another observational study involved the use of clobetasol propionate 0.05% under occlusion in 28 patients with alopecia areata totalis and alopecia universalis [28]. Eight (28.5%) patients achieved successful growth 6–14 weeks after the start of treatment.

#### ***Versus each other***

A randomized, controlled, investigator-blinded trial compared betamethasone valerate foam and betamethasone dipropionate lotion in patients with mild to moderate patch alopecia areata [29]. Of the 61 patients evaluated, more than 75% regrowth was achieved in 61% of the patients using betamethasone valerate foam, as opposed to 27% of patients using betamethasone dipropionate lotion.

#### ***Versus topical pimecrolimus***

I found one RCT: 100 consecutive patients were enrolled and randomized into four groups; 30 received 1% pimecrolimus cream, 30 received 0.05% clobetasol propionate cream, 20 received placebo, and 20 had half head treatments with pimecrolimus and clobetasol. There was a trend to worse improvement in the placebo group; however, none of the results achieved statistical significance [30].

#### ***Harms***

Side effects of topical therapy include folliculitis, hypertrichosis, acneiform eruption, and the potential for long-lasting local atrophy and telangiectasia [27].

#### ***Comments***

Potent topical steroids such as clobetasol propionate and betamethasone valerate foam may be of benefit in alopecia areata – particularly the newer formulations and in young children who have relatively thin skin. When used, the treatment should be used continuously for a minimum of 3 months.

#### **Psoralein plus ultraviolet A**

Photochemotherapy involves oral ingestion of psoralen capsules before exposure to ultraviolet A (PUVA) radiation. Treatment is performed three times a week, with the dose of UVA being increased gradually.

##### ***Benefits***

I found no systematic reviews or RCTs. A retrospective audit of 10 years of experience with PUVA showed an effective success rate of 6.3% for disease less severe than the alopecia totalis state [31].

Topical PUVA has been used in a small study of 22 patients with alopecia areata, of whom 36% achieved a regrowth of at least 75% of the treated scalp [32].

#### ***Harms***

Potential risks include sunburn, irritation, accelerated photodamage, and subsequent development of lentigo, nonmelanoma skin cancer, and melanoma [31].

#### ***Implications for clinical practice***

PUVA is likely to be beneficial for only a small number of people. The time commitment involved in attending three times a week for up to 6 months and the potential to induce skin cancer make this therapy unattractive to most patients. PUVA is contraindicated in children because of the possible increase in the risk of later



Figure 57.2 Alopecia areata in an ophiasis pattern.

development of melanoma. Topical PUVA remains an option for this group, but larger scale studies would need to be done to assess the efficacy of this treatment modality.

### **Anthralin (dithranol)**

Anthralin (dithranol) therapy is thought to act as a contact irritant and possibly also as an immunomodulator. Case series suggest that it needs to be applied on a daily basis in a sufficiently high concentration to produce skin irritation.

#### **Benefits**

I found no systematic reviews or RCTs. An uncontrolled, unblinded case series including 68 patients with extensive alopecia areata suggested that up to 25% of patients with patchy alopecia areata may achieve regrowth, compared with 14% with hair loss >75%. New hair growth was generally seen within 3 months if the treatment was effective, although it may take more than double this time to achieve a cosmetically acceptable response [33].

#### **Harms**

Side effects include irritation, scaling, folliculitis, and regional lymphadenopathy. Patients need to protect treated areas from sun exposure. Reversible staining of the skin occurs, and contact with the eyes must be avoided [21].

#### **Comments/implications for clinical practice**

Anthralin is less effective than contact immunotherapy, but readily available and simple to prescribe.

### **Topical minoxidil**

#### **Benefits**

I found no systematic reviews.

#### **Versus placebo**

I found 10 RCTs comparing various concentrations of topical minoxidil with placebo. Early reports suggested a significantly increased frequency of regrowth in patchy but not total alopecia areata [34–40], although subsequent RCTs failed to confirm these results [41,42].

#### **Versus betamethasone**

This incompletely reported study suggested that there was a higher response rate to 5% minoxidil than to 0.005% betamethasone

dipropionate. Both were said to be superior to placebo, but strict numbers and statistical analyses were not reported [43].

#### **Harms**

Systemic side effects are rare with topical minoxidil, and are generally only seen when it is combined with penetration enhancers. When used as monotherapy, the very low serum concentrations of minoxidil after twice-daily topical administration produce no serious systemic hypotensive side effects in minoxidil users [44]. Irritant contact dermatitis is seen in fewer than 10%. Allergic contact dermatitis reaction is rare [34].

#### **Comments**

Minoxidil is unlikely to be beneficial. It is a nonspecific hair-growth stimulant with an unknown mechanism of action. Any effect it may have in alopecia areata is not immunologically based.

### **Cryosurgery**

#### **Benefits**

I found no systematic reviews and no RCTs. I found a single partially controlled case series of 112 patients with patchy alopecia areata covering <25% of the scalp. Seventy-two patients with a total of 237 lesions received a 2–3 s application of a cotton swab dipped in liquid nitrogen [45]. Two freeze–thaw cycles were applied once weekly for 4 weeks. New hair growth was seen in over 60% of the area involved in over 97% of patients treated with liquid nitrogen, which was statistically significant compared with the results of the nontreatment group.

#### **Harms**

Side effects include skin irritation, vesiculation, and blistering. Temporary hyperpigmentation and permanent hypopigmentation can also occur.

#### **Comments/implications for clinical practice**

Cryosurgery is unlikely to be useful. It is not suitable for people with darkly pigmented skin.

### **Aromatherapy**

#### **Benefits**

I found one RCT. The use of aromatherapy was compared with carrier oils alone in a randomized, double-blind, controlled trial over 7 months [46]. Treatment with the essential oils cedarwood, lavender, thyme, and rosemary oils massaged into the scalp every night was seen to be significantly more effective than treatment with carrier oil alone, with an improvement rate of 44%. Although the patients were randomized, treatment groups were small and disease severity was not specified. This result awaits confirmation.

#### **Harms**

None were found.

#### **Comments/implications for clinical practice**

Aromatherapy is unlikely to be successful.

## **What are the management options for severe chronic alopecia areata (including alopecia totalis and universalis)?**

### **Case scenario 57.2**

Michael is 15 years old. At the age of 13, he developed a solitary patch of alopecia areata. Two weeks after an intradermal injection

of triamcinolone, 5 mg/mL, he developed diffuse generalized hair shedding and within 10 days was totally bald (Figure 57.2). Three months later he began to lose his eyebrows and eyelashes, and ultimately every hair on his body was lost. Unable to cope with the teasing at school, he had not attended for the previous 8 weeks. A general assumption by his teachers was that he was away from school receiving chemotherapy.

## Topical immunotherapy

### Benefits

I found one systematic review, no RCTs, but numerous case series [22,23,47,48]. Response rates for patients with severe disease vary from 2 to 50%.

### Harms

These are identical to those listed for topical immunotherapy for patchy alopecia areata.

### Comments/implications for clinical practice

In all the case series reported, patients with severe alopecia areata and in particular alopecia totalis/universalis, responded less frequently to topical immunotherapy. While the response rates are lower when patients have severe alopecia areata, these patients are often highly motivated and prepared to trial the therapy regardless. A minimum trial of 6 months is required. Initial therapy to half the head and only treating the opposite half after demonstrable regrowth is advocated.

## Systemic corticosteroids

Oral prednisolone or dexamethasone or intravenous methylprednisolone will stimulate hair regrowth in most, but not all, patients if used at a high enough dosage. It has been suggested that the initial dose threshold for oral prednisolone is 0.8 mg/kg, which is then decreased slowly over 6–8 weeks. Pulse therapy can also be considered in these patients.

### Benefits

I found no systematic reviews. A placebo-controlled study evaluated the efficacy of pulse oral prednisolone therapy in severe alopecia areata. The regimen involved 200 mg oral prednisolone once a week for 3 months. Of the 84 patients recruited, 40% experienced significant hair regrowth at the end of 3 months, compared with none in the placebo group. Indicators of poor outcome in this study included atopy, nail involvement, multiple episodes, and prolonged duration of disease (more than 2 years). Relapse rates after treatment were not commented on in this study [49]. Numerous case series have been reported as well, but these are not directly comparable because of different patient selection, dose scheduling, and duration of therapy. Winter *et al.* [50] reported a case series of 18 patients with prednisolone on alternate days at doses adjusted according to the clinical response (usually two to four times the daily adrenal replacement dose, and up to 80–120 mg on alternate days in unresponsive patients). A progressively increasing dose of prednisolone was required to maintain cosmetically acceptable hair growth, and most patients experienced rapid hair loss after discontinuation of prednisolone therapy [50]. Oral steroids used in combination with topical and intralesional steroids have shown benefit in nonrandomized trials [51]. The use of topical and intralesional steroids allowed for more rapid lowering of oral doses, and thus minimization of side effects. Seven of 15 patients treated with oral

steroids showed regrowth of most or all of their hair, with an average remission of 32 months [52].

### Harms

Weight gain and Cushingoid facies are the main side effects [51]. Prolonged therapy with oral corticosteroids may retard growth, demineralize bones, and lead to premature fusion of the bony epiphyses. Nausea and polymenorrhea can occur with pulsed steroid therapy [52].

### Comments/implications for clinical practice

Many patients who are offered systemic corticosteroids decline to take them because of the potential systemic side effects and the high relapse rate. Around 70–80% of patients do regrow hair following a brief course of systemic corticosteroids, but over 50% of those who regrow hair with systemic corticosteroids relapse on dose reduction or within a few months of ceasing therapy. While around 35–40% of patients have sustained remissions following a course of treatment, a similar number will either have to accept the relapse or consider long-term systemic treatment. Some patients can be managed with low-dosage systemic corticosteroids (5–10 mg per day) or with a steroid-sparing agent. Long-term high-dose systemic corticosteroids are not desirable and are not recommended for alopecia areata. In view of the limited therapeutic alternatives, systemic corticosteroid use is attractive, but clinicians must contemplate how the dosage will be weaned and relapses managed. Patients who require more than 6 weeks of systemic corticosteroids should receive general measures to prevent bone demineralization [53].

## Ciclosporin

### Benefits

I found no systematic reviews or RCTs for oral ciclosporin. In a small case series, six patients received oral ciclosporin, 6 mg/kg per day for 12 weeks [54]. All patients had some regrowth, but cosmetically acceptable regrowth occurred in only two of five patients with alopecia totalis/universalis and in the single patient with patchy alopecia areata. All patients had relapsed within 3 months of stopping therapy. A randomized study of 26 patients with alopecia totalis or universalis compared topical 10% ciclosporin daily with photochemotherapy three times a week and intravenous thymopentin, 50 mg three times a week every 3 months over 9 months [24]. All of the patients had previously been unresponsive to sensitizing therapy for at least 12 months. None of the patients in the study had any cosmetic clinical improvement by the end of the study.

### Harms

In the case series of six patients receiving oral ciclosporin, the side effects were mild and transient [55]. Davies and Bowers. reported on two patients who had first developed alopecia areata while taking ciclosporin [55]. While the precise mechanism is unknown, alopecia areata can occur in patients who are at least partially immunosuppressed.

### Comments/implications for clinical practice

The effectiveness of oral ciclosporin for alopecia areata is unknown. A dosage of 6 mg/kg per day is a high dose of ciclosporin and would require very careful monitoring for renal and other toxicity. The relapse rates on discontinuation of therapy are high, and there is a reluctance to use long-term therapy because of cost and cumulative side effects. Topical ciclosporin is ineffective.



## Methotrexate

### Benefits

I found no systematic reviews or RCTs for oral methotrexate. A number of retrospective case series, using either methotrexate alone or in combination with corticosteroids, including one in children, have suggested a clinical response in a proportion of patients [56,57].

### Harms

The effectiveness of methotrexate for alopecia areata is unknown. The average maximum dosage of 18.9 mg per week is high and would require very careful monitoring for hepatic and other toxicity.

## Azathioprine

### Benefits

I found no systematic reviews or RCTs for oral azathioprine. Azathioprine is commonly used as a steroid-sparing agent in the treatment of autoimmune disease. In one case series, where 20 patients were treated with 2 mg/kg for 6 months, statistically significant improvement in the mean hair score compared with baseline was seen. There was no placebo group control in this study [58].

### Harms

Azathioprine can have serious hemotological toxicity. Pretreatment estimation of the serum trimethypurine methyl transferase is available in most countries and can be used to estimate risk of myelosuppression.

## Other therapies

### Benefits

Alefacept, efaluzumab, etanercept, and adalimumab are not effective in promoting hair regrowth in alopecia areata [59]. In fact, there are numerous case reports of alopecia areata developing in patients being treated with biologics.

Inosine pranobex at a dosage of 50 mg/kg per day for 6 months was ineffective in one series [60] and slightly helpful in another [61].

The combination of SADBE immunotherapy at weekly intervals and interferon alpha  $3.0 \times 10^{-6}$  IU intramuscularly, daily for 15 days, three times a week for 2 weeks, then once a week for 2 months, appeared to be better than SADBE alone [62].

Sulfasalazine was reported as useful in one case series, but this has not been reproduced [63].

### Harms

Flu-like symptoms were observed in patients receiving interferon alpha [62]. No clinically significant side effects attributable to inosine pranobex were reported [61].

### Comments/implications for clinical practice

The low response rate in alopecia totalis should be explained to patients before commencing experimental treatments.

## What are the treatment options for alopecia areata in children?

### Case scenario 57.3

Anthony developed 20-nail dystrophy at the age of 30 months. Six months later he developed a single patch of alopecia areata. Nightly

topical application of 0.05% clobetasol dipropionate cream to the patch led to regrowth within 6 weeks, with no obvious cutaneous atrophy. There was some mild associated hypertrichosis of the forehead, which resolved within 6 months of the cream being stopped.

Anthony had no family history of alopecia areata, and no history of atopy. Three years later he presented again with four patches of alopecia areata, each about 3 cm in diameter.

## Topical corticosteroids

Topical corticosteroids are discussed under the section on patchy alopecia areata.

### Benefits

In an observational study of 48 patients, children aged 3–10 years had a higher response rate to topical corticosteroids than adults did [27].

## Topical immunotherapy

### Benefits

I found no systematic reviews. I found one RCT that involved small numbers of children. Tosti *et al.* [18] compared SADBE, diphencyprone, minoxidil, and placebo, finding a significant relationship between the age of the patients and the results. Complete hair regrowth was seen in 71.3% of adults, but in only 38.9% of children.

I found two case series. Schuttelaar *et al.* [64] treated 26 children with diphencyprone weekly for a period of 3–12 months. Sixteen subjects had alopecia areata totalis, and the others had patchy disease only. Eighty-four percent of the children showed hair regrowth, 32% of the total being cosmetically acceptable. Where treatment failed (0–5% hair growth), it was recommended not to continue treatment for longer than 1 year, as hair growth is not promoted by continued treatment. Orecchia and Malagoli [65] treated 28 unresponsive children under the age of 13 years with SADBE for 12 months. Thirty-two percent of the patients achieved complete or cosmetically acceptable regrowth, and a further 21% achieved significant regrowth.

### Harms

Schuttelaar *et al.* noted the problem of psychological dependence on the diphencyprone in certain children and parents, who asked to continue treatment after regrowth had been achieved, fearing a relapse [64]. As with previous studies, itching, erythema, and scaling were noted side effects. Swelling of regional lymph nodes was common and disappeared after discontinuation of treatment [65].

### Comments/implications for clinical practice

Topical immunotherapy has been used in children as young as 4 years by a number of investigators. Taking into consideration that the development of alopecia areata before the age of 10 years is an independent adverse prognostic indicator, side effects and efficacy appear to be similar to those seen in adults. Efficacy is also influenced by the extent of the disease, associated nail changes, and atopy.

## Topical minoxidil

Topical minoxidil has not been tested in children. Systemic absorption and systemic side effects may be more likely to occur in children.

## Key points

### Patchy alopecia areata

- The spontaneous remission rate in alopecia areata is high, which makes evaluation of treatment in the absence of RCTs very difficult.
- No treatment alters the natural history of alopecia areata.
- I found no good evidence in support of nondrug treatment.
- Small RCTs have shown that intralesional injection of triamcinolone acetonide can effectively stimulate regrowth of patchy alopecia areata. Transient atrophy is common. Treatment can be repeated at 4–6-weekly intervals if necessary. I was not able to find data on long-term efficacy.
- One RCT demonstrated that potent topical corticosteroids are marginally more effective than placebo in patchy alopecia areata when used continuously for a minimum of 3 months. In observational case series, children between the ages of 3 and 10 years appear most likely to respond.
- I found one systematic review based on case series on the use of topical immunotherapy. A number of studies have demonstrated unilateral hair regrowth after unilateral treatment. This protocol has been favored for evaluation of topical immunotherapy because of the inability to blind patients. The systematic review of published case series on the use of topical immunotherapy with diphenylcyclopropenone concluded that 50–60% of patients achieve a worthwhile response. Patients with limited disease have higher response rates than those with alopecia totalis/universalis.
- I found insufficient evidence on the use of topical minoxidil, topical anthralin therapy, PUVA, aromatherapy, cryosurgery, and ciclosporin A.

### Alopecia totalis/universalis

- The prognosis for spontaneous or assisted regrowth is poor.
- In all RCTs, the extent of disease is an adverse prognostic factor for regrowth.
- Systemic corticosteroids can be used, but not for prolonged periods – a tapering schedule and a plan for managing relapses should be thought of from the outset.

### Childhood alopecia areata

- In most RCTs, an early age of onset is an adverse prognostic factor for regrowth.
- Topical corticosteroids therapy may be more effective in children than in adults.
- Intralesional injection of corticosteroids is unsuitable for use in children. Most children will not tolerate repeated injections, limiting the usefulness of intralesional corticosteroids.
- Prolonged therapy with oral corticosteroids may retard growth, demineralize bones, and lead to premature fusion of the bony epiphyses.
- PUVA is contraindicated in children because of the possible increase in risk of future development of melanoma.
- Topical PUVA can be tested in this group.

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# Evidence-based treatment of hirsutism

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## Background

### Definition

Hirsutism is defined as the presence of excess terminal (coarse) hairs in females in a pattern typically seen in adult males [1,2]. Hypertrichosis, unlike hirsutism, is independent of androgen influence and is characterized by the superfluous and uniform growth of nonterminal (vellus) hair over the body, particularly in nonsexual areas [3].

### Incidence/prevalence

Approximately 5–10% of women of reproductive age in the general population are hirsute (assessed as having a Ferriman–Gallwey (FG) score of  $\geq 8$ ) [1–4]. The FG score is a clinical score evaluating and quantifying the amount of hair growth in 11 different body areas [5].

### Etiology

Hirsutism is usually the result of an underlying adrenal, ovarian, central endocrine, or peripheral abnormality. Elevated secretion of androgens, increased bioavailability of testosterone, and increased sensitivity of hair follicles to androgens all contribute to the condition [1,6]. The most common cause of androgen excess is polycystic ovary syndrome (PCOS); 70–80% of patients with androgen excess demonstrate hirsutism [2]. Up to 4% of women are affected by PCOS, in whom hirsutism is the most common clinical manifestation of the elevated androgen levels [7]. Hirsutism is deemed idiopathic when it develops in the absence of excess androgen levels and in conjunction with normal ovulatory function; these findings account for less than 20% of hirsute women [8]. Other causes of androgen excess, such as nonclassic congenital adrenal hyperplasia (1.5–2.5% of cases) [9,10] and androgen-secreting tumors (0.2% of cases) are less common causes of hyperandrogenism. Cushing's syndrome, hyperprolactinemia, acromegaly, and thyroid dysfunction are other rare but possible causes, and certain prescribed drugs, such as anabolic or androgenic steroids, can also cause hirsutism [3,6,11].

### Prognosis

If the underlying cause of hirsutism can be well controlled (e.g., ovarian or adrenal dysfunctions), the hirsutism may resolve or at least be well controlled. As no cause can be identified in idiopathic hirsutism, its prognosis may be poorer, and resolution will depend on hair removal by physical, chemical, or electrical means. Women presenting with hirsutism due to PCOS may not respond well to epilation treatments unless the specific underlying cause is addressed. The correct evaluation and diagnosis of female hirsutism, coupled with the use of combination therapy, can provide adequate results in many patients, although long-term studies are needed to confirm current findings.

### Diagnostic tests

*Hirsutism is a clinical diagnosis.* A European consensus was published on the evaluation of women presenting with excessive hair growth based on a systematic review and discussion of current clinical practice across Europe. The interdisciplinary European expert group developed a diagnostic questionnaire for daily practice [11]. Diagnosing hirsutism requires a medical history, physical examination, and investigations to screen for any risk factors for virilizing disorders, PCOS, or hormonal imbalances. It is also important to consider whether any of the patient's current medications could potentially cause or exacerbate the hirsutism. In the case of rapidly progressing hirsutism, or when there is evidence of further virilization, it is important to eliminate the presence of an androgen-secreting tumor. The severity of hirsutism can be evaluated using the FG score [5,11], although caution is required, as it is a subjective assessment measure and not as readily applicable in women of Asian origin. A popular adoption of the FG evaluates nine, rather than 11, body sites [1,3]. Each body site is scored from 0 to 4 on the basis of the number of coarse hairs present. A score of 8 or more is consistent with the diagnosis of hirsutism. The FG score is also used in monitoring the patient's individual responses to treatment and is helpful for the clinician in evaluating the patient's degree of hirsutism.

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In patients with moderate or severe hirsutism, or in whom other risk factors are present, a screening test for androgen excess is an early morning:

$$\text{Free androgen index (FAI)} = \frac{\text{Total testosterone} \times 100}{\text{Sexual hormone binding globulin (SHBG)}}$$

In addition, dehydroepiandrosterone sulfate (DHEAS) should be measured while performing hormonal diagnostic work-up. Whereas normal total testosterone and DHEAS readings in patients with regular menstrual cycles support the diagnosis of idiopathic hirsutism, normal levels do not eliminate peripheral androgen excess. Hair follicles and sebaceous glands can synthesize androgens de novo or convert circulating androgens to more potent ones. Furthermore, a monthly curve of basal temperature, in combination with a measurement of 17-OH-progesterone (days 20–24), should help exclude the presence of an asymptomatic anovulatory menstrual cycle or late onset adrenogenital syndrome. In patients with hirsutism and irregular menstrual cycles, a thorough endocrinological work-up is essential. The following laboratory tests should be undertaken: 17-OH-progesterone, estradiol, SHBG, prolactin, testosterone (total and free), DHEAS, cortisol, thyroid-stimulating hormone, and serum glucose. Mildly elevated total testosterone levels or FAI unsatisfactory responses to treatment, or the suspicion of another disorder all warrant an early-morning free plasma testosterone test [10,11]. Severely raised total testosterone ( $>19 \mu\text{mol/L}$ ) is suggestive of an underlying neoplasm, with elevated levels of DHEAS indicating an adrenal source. Ultrasonography of the adrenal gland and/or pelvic region can also be helpful in the diagnosis of hirsutism. In the case of PCOS in particular, imaging the ovaries and performing hormonal tests (i.e., the luteinizing hormone/follicle-stimulating hormone ratio) can help confirm or refine the diagnosis.

### Aims of treatment

The aim of treatment is to treat any causal hormonal imbalance and decrease the excessive hair growth of hirsutism, thereby positively affecting the patient's quality of life [12]. The primary goal in the management of hirsutism is to achieve central or peripheral androgen suppression using three groups of drugs: inhibitors of androgen production (oral contraceptives (OCPs), gonadotropin-releasing hormone analogues), peripheral androgen blockers (cyproterone acetate, flutamide, finasteride, and spironolactone) and insulin sensitizing agents (metformin). A combination of pharmacological, physical and chemical treatment regimens can be used, depending on the particular case, to achieve the optimum result for the patient.

### Relevant outcomes

Outcome measures to evaluate the management of hirsutism include clinical evaluation using the FG score, hair density, thickness, and length, or questionnaires [11]. There are few studies employing objective measurements such as a phototrichogram and global photographic evaluation to quantify hair growth changes. In addition, well-designed controlled studies that include assessment of patients' quality of life are needed.

### Methods of search

- Cochrane library.
- Medline search.
- Embase.

- References from reviews on hirsutism and associated clinical conditions.
- Use of professional knowledge of publications in the field.

## Questions

### What are the effects of treatments for a woman with idiopathic hirsutism?

#### Case scenario 58.1

A 25-year-old woman has suffered from excessive facial hair growth since puberty (Figure 58.1). She plucks and waxes regularly to remove unwanted facial hair and has tried electroepilation, which resulted in mild scarring. She is unhappy with the frequency with which she has to carry out these hair removal techniques and with the time involved in treating the relatively large area affected. Dermatological assessment revealed a modified FG score of about 18, with hypertrichosis mainly on the face and less on the upper legs. No other signs of hyperandrogenemia were noted. Following consultation with a gynecologist, PCOS, nonclassic adrenal hyperplasia, androgen-secreting tumors, and prolactinoma were excluded as potential causes of the patient's facial hirsutism.

### Antiandrogens

#### Efficacy

**Cyproterone acetate** There is one systematic review of nine randomized controlled trials (RCTs) using cyproterone acetate to treat hirsutism [13]. Cyproterone acetate combined with estradiol resulted in a subjective improvement in hirsutism in comparison with placebo. No clinical differences in outcome were found between cyproterone acetate and the other medical therapies (ketoconazole, spironolactone, flutamide, finasteride, and gonadotropin-releasing hormone analogues). However, the different drug



**Figure 58.1** A 25-year-old woman with excessive facial hair 2 weeks after waxing.

therapies lead to endocrinological differences in androgen and estrogen levels.

A well-designed ( $n = 134$ ) RCT compared three treatment regimens with cyproterone acetate or drospirenone containing combined OCPs plus spironolactone or cyproterone acetate in women with moderate and severe hirsutism [14]. All three treatment regimens significantly decreased the modified FG hirsutism score, but without significant difference between groups.

**Chlormadinone acetate** The use of combined OCPs containing chlormadinone acetate (CMA) or cyproterone acetate plus ethinyl estradiol (EE) was shown to produce an improvement of patients' hirsutism in 36% of cases [15]. CMA-containing combination OCPs have proved similarly effective as cyproterone acetate/EE in women with androgen-related skin and hair conditions. A small single-center clinical study on young nonobese women with PCOS ( $n = 15$ ) receiving a six-cycle treatment with EE30 CMA demonstrated an efficacious improvement of hyperandrogenic symptoms compared with a matched age group of nonobese no OCP-PCOS women [16]. Hirsute women showed significant improvement of sexual life quality and self-esteem evaluated in a small noncontrolled clinical study of hirsute women receiving for 9 months an OCP containing EE/CMA [17].

**Spironolactone** One systematic review of the use of spironolactone in the treatment of hirsutism and/or acne was found, which included nine RCTs [18]. The review concluded that 6 months' treatment with spironolactone 100 mg/day was associated with a statistically significant subjective improvement in hair growth and a decrease in the FG score in comparison with placebo. Overall, the authors stated that individual study data indicated some superiority of spironolactone over other drugs, but owing to small and scarce studies these results cannot be generalized.

Spironolactone 100 mg/day in the treatment of hirsutism has also been shown to be more effective than finasteride 5 mg/day and low-dosage cyproterone acetate 12.5 mg/day (first 10 days of cycle) up to 12 months after treatment [6]. An open-label trial of 109 women demonstrated that low-dose spironolactone successfully improved hirsutism in 72% of women treated [14]. Another open-label trial comparing the efficacy of spironolactone and metformin in 82 young women with PCOS found that the two drugs were similarly effective in the management of PCOS, although spironolactone was more effective in the treatment of hirsutism [6].

A systematic review and meta-analysis on RCTs investigating antiandrogens for the treatment of hirsutism with 12 eligible RCTs (18 comparisons) of relative low methodological quality concluded that there is only weak evidence that antiandrogens are mildly effective agents for the treatment of hirsutism [19]. For clinical practice it is important to note that spironolactone or finasteride in combination with contraceptives or flutamide with metformin appear superior to monotherapy with contraceptives and metformin, respectively.

**Flutamide and bicalutamide** Flutamide was found to be more effective than finasteride in the treatment of hirsutism. An RCT comparing low-dose flutamide, finasteride, ketoconazole, and cyproterone acetate–estrogen regimens in the treatment of 66 hirsute women showed that flutamide and cyproterone acetate, combined with estradiol, were the most effective and well tolerated of the treatments studied [20]. An RCT compared the efficacy of flutamide and spironolactone plus Diane 35 (cyproterone), Dianette (2 mg cypro-

terone acetate and 35 µg EE) in the treatment of hirsutism [21]. In this study of 80 patients, the FG score decreased significantly and to similar levels in both treatment groups, suggesting that the two therapies are similarly effective in the treatment of hirsutism.

Long-term efficacy and tolerability of flutamide evaluated in a prospective observational study showed that although flutamide was very effective in treating hirsutism, frequently occurring adverse effects lead to low long-term compliance [22].

The efficacy of low-dosage bicalutamide (25 mg/day) in the treatment of hirsutism was investigated in a small open-label study of 42 women [23]. Clinical improvement in the degree of hirsutism was observed in all patients, with the mean modified FG score decreasing from  $22.0 \pm 5.1$  to  $8.6 \pm 3.5$  after 6 months' treatment ( $P < 0.0001$ ). Hair density was visibly reduced; with a reduction in the FG score of  $41.2 \pm 11.4\%$  seen at 3 months and of  $61.6 \pm 11.1\%$  at 6 months.

### Drawbacks

The spectrum of adverse effects of antiandrogens includes headache, nausea, weight gain, depression, fatigue, breast symptoms, menstrual irregularity, and sexual dysfunction, but there is not enough evidence to compare the differences of adverse events between the different therapeutic options [13]. Spironolactone may lead to polymenorrhea and hyperkalemia [6].

### Comments/implications for clinical practice

Antiandrogens can produce statistically significant improvement in hair growth and decreases in FG scores. However, small study sizes and a lack of standardized assessment and objective measurements of improvements in hirsutism mean that the results are difficult to interpret. Clinical impressions of treating doctors are thinning of hair shaft diameter and reduction of hair regrowth rate leading clinically to improved, but most often not satisfactory, results for the concerned women. Further studies are required in order to compare efficacy and safety profiles between drug therapies for hirsutism using objective measurements such as hair density, hair thickness, and hair growth rate. Antiandrogens should always be administered in women of childbearing age along with reliable contraception owing to the risk of feminization of a male fetus in case of pregnancy under antiandrogens.

### Enzyme inhibitors: finasteride

#### Efficacy

The 5 $\alpha$ -reductase inhibitor finasteride has been evaluated for the treatment of hirsutism in many randomized and observational trials. The results have shown that finasteride can lower hirsutism scores by 30–60%, in addition to reducing the average hair diameter [19,24].

In an RCT comparing low-dose flutamide, finasteride, ketoconazole, and cyproterone acetate–estrogen regimens in the treatment of 66 hirsute women, finasteride treatment significantly reduced FG scores (–44%), hair diameter (–16%), and daily hair growth rate (–27%) [25]. Although finasteride had the slowest onset of action of the drugs studied in the trial, it was still highly effective, with the hair diameter at the end of treatment similar to that in the other therapies studied. Furthermore, finasteride was associated with fewer side effects.

In a similar trial of 41 women with idiopathic hirsutism, the short-term results of treatment with cyproterone acetate, finasteride, and spironolactone were similar, but spironolactone demonstrated a higher efficacy over a longer time period [24]. In a small

clinical study, investigation of the efficacy and safety of finasteride (5 mg/day) plus flutamide (125 mg/day) combination therapy in unselected women with hirsutism ( $n = 44$ ) revealed that flutamide is more effective than finasteride and the combination of these two drugs is not better than flutamide alone, but better than finasteride in hirsute women [26].

### **Drawbacks**

Finasteride may cause breast enlargement, breast tenderness, and rash.

### **Comments/implications for clinical practice**

Although finasteride has been shown to be effective in the treatment of hirsutism, it is not licensed for the condition. It is also contraindicated in women who wish to become pregnant or are potentially pregnant, as it can cause feminization of the male fetus. Women treated with finasteride should therefore also be given appropriate and safe contraception.

## **What are the effects of topical treatments for facial hirsutism?**

### **Enzyme inhibitors: eflornithine**

#### **Efficacy**

The efficacy of eflornithine in the treatment of facial hirsutism has been evaluated in two multicenter, randomized, double-blind, placebo-controlled trials including 596 patients, which were not published separately but only as pooled analysis. [27]. Facial hirsutism significantly improved within 8 weeks of treatment with eflornithine. After 24 weeks of treatment, 70% of the patients treated showed some improvements, with 32% of patients said to be clinically improved in comparison with only 8% in the placebo group.

Combination therapy with eflornithine cream plus laser epilation can be effective and results in more rapid hair removal in comparison with laser monotherapy [28,29]. Further long-term prospective trials are needed in this area. In addition, use of topical eflornithine has been shown to significantly improve women's emotional burden by excessive hair compared with those receiving placebo [30].

### **Drawbacks**

The most common adverse events associated with eflornithine treatment are mild and skin related, including burning, tingling, stinging, erythema, and rash at the site of application (2–7% over a 12-month observation period. All of these are mild, transient, and resolve without dose reduction and without medical intervention.

### **Comments/implications for clinical practice**

Eflornithine is simple to apply and can therefore be readily incorporated into patients' existing daily skin-care regimens. Treatment with eflornithine can be used alongside medical treatments or mechanical hair removal methods. Treatment with eflornithine is not indicated during pregnancy and lactation. It should be noted that the benefits of treatment start to diminish 8 weeks after therapy is discontinued.

## **What are the effects of alternative methods of epilation for treating hirsute women?**

### **Electroepilation**

#### **Efficacy**

No systematic reviews or RCTs were found. Richards *et al.* reported the results of over 35 000 h of electroepilation treatment in 281

women over a 4-year period [31]. The study found that electroepilation was beneficial in controlling facial hirsutism, with 93% of patients showing improvement, with no evidence of scarring. The best results were obtained when electroepilation was combined with medical treatment to resolve any androgen excess. Based on observations from 13 years and 140 000 h of experience, the blend method is reported to be the most effective method for permanent hair removal [32]. In the blend method, heat is created through the modulation of a high-frequency current, leading to thermal injury of the hair follicle with subsequent destruction. Although permanent hair removal can be achieved in some cases, the success of the technique ultimately relies on the skill of the operator.

### **Drawbacks**

Electroepilation can cause temporary pain, erythema, and edema. Scarring, keloid formation, and postinflammatory pigment changes are also possible. There is insufficient evidence to recommend electroepilation as a method superior to other epilation techniques.

### **Comments/implications for clinical practice**

Electroepilation may take up to 24 months to be effective, and its success is dependent on many factors, such as previous treatments, hair type, and operator skill. There is an increased risk of scarring if probing is inaccurate, if too much current is used, or if hygiene or aftercare are inadequate.

### **Photoepilation**

#### **Efficacy**

One systematic review was found including 11 RCTs, none of which were of high quality. There appeared to be a short-term effect of approximately 50% hair reduction with alexandrite and diode lasers up to 6 months after treatment, whereas there was little evidence for an effect with intense pulsed light, neodymium:yttrium-aluminum-garnet (Nd:YAG) or ruby lasers [33]. Long-term hair removal was not reported for any treatment. According to the authors, pain, skin redness, swelling, burned hairs, and pigmentary changes were the most frequent reported adverse effects.

In an RCT of 88 women with PCOS-related hirsutism, 6 months of photoepilation significantly reduced the severity of facial hair and lowered depression scores and anxiety ratings compared with controls [33]. In a retrospective study using a solid-state 100 nm pulsed near-infrared diode laser system in 242 patients, retrospective analysis of patient questionnaires revealed that a reduction in pigmented hair was achieved after an average of 1.97 treatments and maintained for a mean period of 8.1 months [34,35]. The habitual hair-plucking interval was also increased from a mean of 3.69 days before treatment to 15.19 days after laser epilation.

In an RCT of single treatment sessions using an alexandrite laser, a 40% reduction in hair growth was seen 6 months after treatment [35]; and in a prospective trial using an Nd:YAG laser, a single treatment session with the laser and topically applied carbon dye resulted in greater hair reduction in comparison with laser alone [36].

Comparison of efficacy and safety of intense pulsed light (IPL) versus long-pulsed diode laser (LPDL) in a well-defined group of hirsute women ( $n = 31$ ) with normal testosterone levels showed that patients responded equally well to IPL and LPDL treatments with reduction of excessive facial hair growth but with declining efficacy over 6 months [37].

In a small RCT in hirsute women, use of IPL proved to be an efficient tool to eliminate white hair, an effect which could be





**Figure 58.2** Central hair thinning in a 32-year-old woman with PCOS, obesity, and hyperinsulinemia.

enhanced by coloring the white hair prior to use of IPL technology [38].

#### **Drawbacks**

Photoepilation can cause edema, erythema, pain, hypopigmentation, and hyperpigmentation. Rarely, increased hair growth at the treated site has been reported.

#### **Comments/implications for clinical practice**

Further long-term RCTs and comparative studies are needed to establish the benefits of photoepilation. With the development of lasers and IPL technology to specifically target hair follicles, large areas can be treated rapidly, and long-term hair-free intervals can be achieved, although permanent hair loss is rare.

### **What are the effects of treatments for women with hyperinsulinemia?**

#### **Case scenario 58.2**

A 32-year-old woman consulted her dermatologist for scalp hair loss (Figure 58.2). Clinical examination revealed female-pattern hair loss. She reported that she felt uncomfortable in the public due to her excessive body hair and that recent weight gain had added to her distress. Her menstrual cycle was irregular, with cycles ranging from 25 to 38 days. She was referred to a gynecologist who diagnosed PCOS. The patient's body mass index (BMI) was approximately 31, and investigations revealed hyperinsulinemia.

#### **Insulin-sensitizing agents**

##### **Efficacy**

A systematic review and meta-analyses of RCTs of metformin or thiazolidines for the treatment of hirsutism for which 16 studies of low to very low quality were eligible demonstrated that insulin sensitizers provide limited or no important benefit for women with hirsutism [36].

There is one systematic review including six trials, four of which compared metformin versus OCP (104 participants) and two of which compared OCP combined with metformin versus OCP alone (70 participants). Limited data demonstrated no evidence of difference in effect between metformin and the OCP on hirsutism

and acne. However, there was a benefit for the women after a 12-month treatment with the OCP with an improvement in menstrual pattern and serum androgen levels compared with metformin; but metformin treatment results in a reduction in fasting insulin and lower triglyceride levels than with the OCP [39].

A small RCT of metformin was carried out to assess the effects of metformin on hair growth [6]. Sixteen women with PCOS and hirsutism were enrolled into a 14-month double-blind, placebo-controlled crossover study. Throughout the study, the severity of hirsutism was assessed using the FG score, patient self-assessment, and growth velocity. Metformin treatment led to significant improvements in the FG score and patient self-assessment. Growth velocity in millimeters per day at the end of each phase was also improved. The authors concluded that metformin treatment in this patient group led to a clinically and statistically significant improvement in hair growth in comparison with placebo.

An RCT with hirsutism as the primary end point compared the efficacy of metformin with combined EE and cyproterone acetate [40]. Patients with PCOS ( $n = 52$ ) received either metformin (500 mg, three times daily) or Diane 35, Dianette (EE 35 µg and cyproterone acetate 2 mg) for 12 months. Objective and subjective methods of evaluating hirsutism and patients' self-assessment scores were used. Metformin treatment resulted in greater improvements in the FG score and patient self-assessment scores. Both treatments were moderately effective in reducing the hair diameter at multiple anatomical sites. The data suggest that hirsutism may be effectively treated by reducing hyperinsulinemia.

In an open-label study comparing the efficacy of metformin with spironolactone in 82 women with PCOS, both treatments significantly improved hirsutism scores, but spironolactone was more effective in slowing hair growth [6].

Recently, a prospective observational study investigated 45 lean PCOS patients who received EE/drospirenone (DRSP) ( $n = 25$ ) or EE/DRSP plus metformin ( $n = 20$ ) and 45 BMI-matched healthy controls. EE/DRSP alone or in combination with metformin improved clinical and biochemical hyperandrogenism in lean PCOS. Insulin sensitivity was not affected by EE/DRSP alone, in contrast to a combination of EE/DRSP with metformin [41].

#### **Drawbacks**

Metformin can cause nausea and vomiting, taste disturbances, and loss of appetite. Rosiglitazone can cause anemia, hypercholesterolemia, flatulence, nausea, vomiting, and gastritis. In September 2010 the European Medical Agency decided to suspend the market authorization of rosiglitazone, while the US Food and Drug Administration decided to restrict the use of rosiglitazone, because rosiglitazone might be associated with an increased risk of ischemic heart disease [42].

#### **Comments/implications for clinical practice**

There are several small RCTs suggesting significant improvement; however, they are based upon a low number of subjects. Even if no general conclusions for clinical practice can be drawn from such small RCTs, their validity should be checked in larger controlled studies as the primary outcome of reduction in hair growth is key for counseling patients affected by hirsutism.

The hair-growth cycle is relatively long, and the potential effects of the drugs studied should not be evaluated with less than 12 months of treatment. Future trials of longer duration, therefore, need to be carried out in order to provide adequate data to inform clinical practice.



## Key points

- Combined OCPs containing cyproterone acetate plus EE or CMA are effective for treating women with idiopathic hirsutism.
- Insulin-sensitizing agents (e.g., metformin) are effective for treating hirsute women with PCOS. Metformin led to a greater improvement in hirsutism compared with EE 35 mg plus cyproterone acetate 2 mg or placebo.
- Photoepilation has been shown to reduce the density of dark hairs. Better results were obtained with alexandrite, diode, or ruby lasers than with the Nd:YAG laser.
- Topical use of the enzyme inhibitor eflornithine has been clinically proven to slow down the rate of hair growth. Combination therapy with eflornithine cream and laser epilation results in better hair removal than laser monotherapy.

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# Focal hyperhidrosis

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## Background

Sweating fulfills several important functions. Sweat is produced by eccrine and apocrine sweat glands, of which the eccrine type is the most numerous. Sweating plays a key role in thermoregulation, whilst localized sweat production enhances grip of, for example, palms. Sweat produced by apocrine sweat glands (e.g., axillae, groin) accounts for odor generation, though their role in humans is not entirely clear. Excessive sweating, or hyperhidrosis, can have a profoundly detrimental physical and psychological impact on those affected [1,2]. Hyperhidrosis is possibly undertreated, with many of those affected never seeking professional help [3].

## Definition

The amount of sweating depends on, for example, environmental factors and the physical and emotional state of the patient [4]. Consequently, there are no widely accepted diagnostic cut-offs for diagnosing hyperhidrosis. This limitation remains a great challenge for those diagnosing, treating, and researching the condition. Sweating is typically categorized as being focal (commonly axillary, palmar, and/or plantar) or generalized, and either primary (i.e., idiopathic, when it tends to be focal) or secondary (where there is an identifiable underlying cause, where the sweating is often generalized).

## Incidence/prevalence

An epidemiological study from the USA estimated the prevalence of hyperhidrosis at 2.8%, most frequently affecting those between 18 and 54 years of age with an average age of onset of 25 years [3]. Studies from North America and South Korea suggest that those with a positive family history have a lower age of onset [4,5]. Results from various epidemiological studies are variable, which possibly reflects inconsistencies in the methods of diagnosis and inherent heterogeneity between different study populations.

There is no reliable evidence for gender differences in terms of incidence/prevalence, although there is some evidence for differences in the types of hyperhidrosis with which people present [4].

## Etiology

Generalized hyperhidrosis can be primary or secondary to a range of underlying conditions such as malignancies, endocrine abnormalities, infections, or neurological diseases. Focal hyperhidrosis, in contrast, is most commonly a primary condition, although there are exceptions, such as Frey's syndrome (gustatory sweating secondary to facial nerve damage, commonly following parotid gland surgery) [6]. The high rate of affected first-degree relatives amongst those with hyperhidrosis has led to suggestions of a genetic basis [7]. The cause of primary hyperhidrosis remains unclear in most instances, but there is limited evidence that the eccrine glands in those with hyperhidrosis differ functionally from those unaffected by the condition [8].

## Prognosis

No good data are available on the prognosis of focal hyperhidrosis.

## Diagnostic tests

In the absence of reliable diagnostic cut-offs, diagnosis of hyperhidrosis is generally based on the history and examination of the individual, sometimes coupled with the use of one or more methods of quantification that can be objective or subjective.

Several objective methods of quantification exist, which tend to be used in research rather than in the clinical setting. One of the most common is gravimetry, which involves weighing the amount of sweat produced over a specific time period, typically through the use of filter paper that is in contact with skin. The surface area that produces sweat can also be visualized; for example, through starch-iodine or ninhydrin testing [9,10]. Additionally, the rate of water loss from the skin surface can be measured through the use of an evaporimeter [11].

Subjective methods of quantification allow a measure of the impact that the hyperhidrosis has on the individual. The dermatology life quality index has been used to assess hyperhidrosis, as have hyperhidrosis-specific questionnaires such as the hyperhidrosis

disease severity scale (HDSS) and the hyperhidrosis impact questionnaire (HHIQ) [3,12,13].

No single method is ideal, but coupled with the thorough assessment of the individual, the above methods of quantification can provide helpful information.

### Aims of treatment

The aim of treatment is to reduce the amount of sweating and to produce patient satisfaction.

### Relevant outcomes

Relevant outcome measures for the success of treatment are patient satisfaction and reduction in sweating as measured objectively and/or subjectively.

### Methods of search

Central, Medline, Embase, and Liliacs were searched for relevant articles. The last search for databases (see Appendix 59A) was June 2012. Additional supplementary searches were conducted in Central and PubMed in September 2012.

## Questions

### Which interventions reduce sweating effectively in patients with axillary hyperhidrosis?

#### Case scenario 59.1

A 24-year-old female patient presents to the outpatient department with excessive axillary sweating since her early teens. She has to change her clothes several times each day. Her clothes are heavily sweat stained around both axillae.

#### Aluminum chloride

Topically applied aluminum salts are some of the commonest treatments for hyperhidrosis. It has been suggested that long-term application leads to structural changes in the eccrine sweat glands and ducts, although the mode of action remains debated [14].

#### Benefits

There are no randomized controlled trials (RCTs), but there are some published case series. In a study by Scholes *et al.*, 65 patients were treated with 20% aluminum chloride hexahydrate in absolute alcohol, applied under occlusion nightly to dry axillae for seven nights and as required thereafter. Nearly all participants (64/65) achieved “complete control” of their hyperhidrosis at 12-month follow-up [15].

In a study by Brandrup and Larsen, 23 females with axillary hyperhidrosis were treated with 25% aluminum chloride solution with ( $n = 11$ ) and without ( $n = 12$ ) occlusion. Sweating was reduced by 60–80% both at rest and during exercise in both groups as measured by gravimetry [16]. Graber reported comparably successful treatment of axillary hyperhidrosis when using a 30% aluminum chloride solution ( $n = 10$ ) [17].

#### Harms

No serious adverse effects were reported with aluminum chloride. Skin irritation was reported by almost half of patients in the study by Scholes *et al.* when using the alcohol-based aluminum chloride solution, which in most cases was relieved by the topical application of 1% hydrocortisone [15]. In the study by Brandrup and Larsen,

itching was reported by all 23 patients, leading to discontinuation of treatment in two individuals. Occlusion was not tolerated by any patient [16].

#### Comments/implications for clinical practice

Despite the absence of good RCTs, 10–30% topical aluminum chloride is likely to be effective. It is often first-line treatment in axillary hyperhidrosis as it is readily available and relatively easy to use. There is a trade-off between adverse effects (commonly local skin irritation) and efficacy.

#### Botulinum toxin A

Botulinum toxin type A (BTX-A) is a bacterial toxin that can be injected into the deeper parts of the skin where the eccrine glands are located. It blocks acetylcholine release from cholinergic presynaptic vesicles, thus leading to chemodenervation of the eccrine glands and subsequently reduced sweat production [18]. Several brands of BTX-A are now available, including Botox® (or onabotulinumtoxinA) and Dysport® (or abobotulinumtoxinA) [19].

#### Benefits

There are no good systematic reviews available, though there are several RCTs. One large double-blind RCT by Lowe *et al.* ( $n = 322$ ) compared BTX-A (Botox) 75 U/axilla, 50 U/axilla and placebo over 1 year; 75% of BTX-A treated patients showed a greater than two-point improvement in the four-point HDSS questionnaire, versus 25% in the placebo group [20]. Median effect duration was 182 days, 159 days, and 62 days for the 75 U, 50 U, and placebo groups respectively. No significant difference was observed between the 75 U and 50 U groups in terms of HDSS improvement or duration of treatment effect.

In another RCT, 50 U of BTX-A (Botox) was used, where a  $\geq 50\%$  reduction in axillary sweating was found in 95% versus 32% of patients in the treatment and placebo groups respectively at week 1, and 82% and 21% at week 16 post BTX-A injection [21]. Longer term follow-up of a small proportion of subjects ( $n = 12$ ) from the same cohort over 18 months suggested the effect of BTX-A injections does not diminish significantly with repeated injections, although the duration of remission following injection was variable [22].

Another RCT evaluated 50 U BTX-A (Botox) in 207 subjects over 16 months. Response rates (as defined by a reduction of 50% as assessed by gravimetry 4 weeks post-treatment) were 96.1%, 91.1%, and 83.3% after the first, second, and third injections respectively. After the second injection, the mean duration of response was 30.6 weeks, with no anti-drug antibodies detected [23].

Heckmann and Plewig investigated the effect of 100–200 U BTX-A (Dysport) in 145 subjects in a double-blind RCT where each patient acted as their own control. At 2 weeks, a 50% reduction in sweating was achieved in 92.4% of patients receiving 200 U, 89% with the 100 U group, and 15.2% with placebo [24]. There was no statistically significant difference between 200 U or 100 U. A smaller ( $n = 43$ ) randomized unblinded study similarly found no significant difference in terms of efficacy between 100 U and 200 U Dysport [25].

#### Harms

There is no good evidence for systemic side effects: 5% of patients in one BTX-A trial reported increased sweating at non-treated sites post-injection (compensatory hyperhidrosis (CH)), versus none in

the placebo group [21]. In another study, 4.3% of patients reported CH [23].

Lowe *et al.* reported only pain as an adverse effect of axillary BTX-A injection, occurring in between 8 and 12% of patients depending on the study group (including placebo). The mean duration of pain was 2.4 days post injection [20]. One double-blind RCT compares BTX-A (Botox) reconstituted in lidocaine versus saline placebo ( $n = 29$ ) and found reduced pain scores for the axillae where lidocaine was used [26]. A double-blind placebo-controlled RCT evaluated topical tetracaine versus placebo before BTX-A (Dysport) injections, in which all patients reported less pain in the tetracaine pretreated axillae [27]. Another randomized study ( $n = 31$ ) further demonstrated reduced pain scores during BTX-A injections where the axillae is cooled for 1 minute pre-injection as compared with no cooling [28].

There is a theoretical risk of anti-BTX-A antibody formation, but this appears not to be an issue over 52 weeks in the studies by Lowe *et al.* [20] or Naumann *et al.* [23].

#### Comments/implications for clinical practice

Botox 50 U or Dysport 100 U per axilla appears to be effective in treating axillary hyperhidrosis. Pain on injection is common. BTX-A injections may be repeated as the patients relapse, but the intervals need to be adapted to the response of that individual.

### Oral anticholinergics

#### Benefits

Oral anticholinergics act on the same cholinergic fibers innervating eccrine glands that are blocked by BTX-A. There are no systematic reviews on their use in axillary hyperhidrosis. One small RCT ( $n = 41$ ) evaluating oral 50 mg methanthelinium bromide (Vagantin®) demonstrated a sweat rate reduction after 4 weeks as assessed by gravimetry: from  $89.2 \pm 73.4$  mg/min to  $53.3 \pm 48.7$  mg/min [29]. A double-blind RCT ( $n = 50$ ) compared the anticholinergic agent oxybutynin (dose increased incrementally up to 5 mg twice daily) with placebo in subjects with axillary or plantar hyperhidrosis and reported an improvement both in terms of level of sweating and in quality of life [30].

#### Harms

In the above oxybutynin study, 34.8% of subjects reported moderate–severe dryness of the mouth at 6 weeks [30]. Dry mouth was also the most commonly reported adverse effect in the study of methanthelinium bromide [29].

#### Comments/implications for clinical practice

At present, more evidence on safety/efficacy from larger trials is needed before reliable recommendations of anticholinergic agents can be made in the treatment of axillary hyperhidrosis.

### Iontophoresis

#### Benefits

There are no good RCTs on the use of iontophoresis for the treatment of axillary hyperhidrosis. Akins *et al.* evaluated the effect of a direct-current device for the treatment of hyperhidrosis [31]. Axillae of eight subjects were treated, with the contralateral axilla acting as a control. A 50% reduction in sweating was observed in three of eight axillae after 2 weeks of treatment as assessed through starch–iodine testing.

#### Harms

Akins *et al.* reported cases of skin discomfort during application of current and more rarely vesicle formation and scalding following treatment [31].

#### Comments/implications for clinical practice

There is at present little evidence that tap-water iontophoresis works in axillary hyperhidrosis. Anatomical factors mean application of current at this site might be less practical when compared with, for example, palms and soles.

### Destructive treatment strategies

Several surgical strategies exist for treating axillary hyperhidrosis, although they are not as widely used as the above treatment modalities. The principle is to remove or induce damage to the eccrine sweat glands.

#### Benefits

Rompel and Scholz compared subcutaneous curettage ( $n = 90$ ) with BTX-A (100 U Botox) injections in patients with axillary hyperhidrosis ( $n = 23$ ) [32]. The two treatments were comparable in terms of patient satisfaction: 66.3% of patient undergoing curettage and 60.8% of subjects receiving BTX-A reported the treatment as “good” or “very good” at the end of the observation period (28.2 months and 16.1 months for each respective treatment). A case-series of 28 patients undergoing axillary curettage by Darabaneanu *et al.* found a 70% reduction of sweating (as assessed by gravimetry) at 1 month and 58% at 1 year post-treatment [33]; 60.7% of subjects found the treatment “satisfactory,” “good,” or “excellent.”

Hasche *et al.* performed liposuction of the axillae in a series of 20 patients where 18 patients reported the outcome as “good” and one as “very good” 2–3 months post-treatment [34].

Glaser *et al.* evaluated a proprietary microwave device that induces thermal damage to eccrine glands ( $n = 120$ ) [35]. No significant difference was observed between treatment and placebo in the proportion of patients achieving a 50% reduction in sweating. However, there was a significant difference between patients achieving an improvement in HDSS score of 1 or 2 at 6-month follow-up (67% and 44% of subjects in the treatment and placebo groups respectively).

Bechara *et al.* hypothesized that treatment with an 800 nm diode laser might reduce axillary hyperhidrosis through disruption of sweat glands [36]. However, no difference was found between laser and sham treatment ( $n = 25$ ) [36].

#### Harms

Complications, such as infection, partial epidermal necrosis, and hematoma formation, were reported in 17.8% of patients who had subcutaneous curettage in the study by Rompel and Scholz [32]. Pain and hematoma formation were reported in the study evaluating axillary liposuction [34]. The most commonly reported adverse event in the microwave device study was altered sensation (9.9% of treated subjects), which resolved in all cases [35].

#### Comments/implications for clinical practice

There is insufficient evidence to support axillary curettage, liposuction, microwave devices, or laser therapy in the treatment of axillary hyperhidrosis. Side effects are potentially serious.

### Sympathectomy

Video-assisted thoracoscopic sympathectomy (VATS) involves disruption of the sympathetic innervation to the thoracic sympathetic



chain supplying the upper limbs and/or face. It is performed under general anesthetic.

### Benefits

In one study by Munia *et al.*, patients ( $n = 62$ ) were randomized to undergo denervation of T3–T4 or T4. At 6 months, 28/32 of those in the T3–T4 groups and 29/30 in the T4 group were “completely satisfied” with the outcome [37].

A retrospective study by Herbst *et al.* of 270 patients having undergone T1–T4 sympathectomies includes 39 patients with axillary hyperhidrosis [38]. Some degree of immediate improvement postoperatively was reported by 77%. Long-term satisfaction (follow-up 9 months–27.1 years) was significantly lower in subjects with axillary hyperhidrosis (33% “satisfied,” 46% “partially satisfied”) compared with patients with hyperhidrosis elsewhere.

### Harms

CH was reported by all subjects undergoing a T3–T4 sympathectomy, whilst the equivalent number was 43.3% in the T4 group [39]. Herbst *et al.* found that the main reason for being dissatisfied was postoperative CH/gustatory sweating, dry hands, and Horner’s syndrome. Overall, 67.4% patients reported CH, 50.7% gustatory sweating, and 2.5% Horner’s syndrome [38].

### Comments/implications for clinical practice

There is insufficient evidence to support sympathectomy for axillary hyperhidrosis. Data available suggest adverse effects such as CH and gustatory sweating are relatively common, though prospective long-term studies are needed.

## Which interventions reduce sweating effectively in patients with palmar hyperhidrosis?

### Case scenario 59.2

A 22-year-old male electrician complains of severe palmar sweating that interferes with his work. Palms are visibly wet at rest.

### Topical agents

#### Benefits

A double-blind RCT of 26 patients with palmar and/or plantar hyperhidrosis demonstrated an improvement in 24/26 patients after topical treatment with 5% methenamine (a formaldehyde-releasing compound, that possibly acts through causing blockage of sweat ducts). Results were generally less favorable for palms than for soles [40].

A further double-blind RCT ( $n = 109$ ) compared 5% methenamine with placebo for palmar and plantar hyperhidrosis. Using a 0–4 graded scale (0 being mildest), there was a significant improvement in sweating (palmar and plantar results pooled) with methenamine (3.2 at baseline, 1.4 post-treatment) compared with placebo (3.2 at baseline and 2.5 post-treatment). Of the patients in the treatment group, 71% rated it as “good” or “excellent” (vs 19% for placebo) [41].

A higher concentration of methenamine was used in a study by Phadke *et al.* that compared 10% methenamine, 5% glutaraldehyde, and tap water iontophoresis. “Good” or “excellent” results were reported by 19/20 of those treated with methenamine, 13/20 treated with glutaraldehyde, and 11/20 treated with iontophoresis after 4 weeks [42].

One study compared topical 20% tannic acid with iontophoresis for palmar hyperhidrosis but found no improvement with the former [43].

Goh compared topical aluminum chloride 20% in an alcoholic base with placebo in a single-blinded fashion ( $n = 12$ ), with each patient acting as their own control. Mean sweating decreased from 79.9 g/(m<sup>2</sup>h) water to 51.4 g/(m<sup>2</sup>h) water, whilst the equivalent figures for the placebo side were 77.9 g/(m<sup>2</sup>h) and 77.7 g/(m<sup>2</sup>h) water [44].

### Harms

No adverse effects were reported with methenamine in the study by Bergstresser and Quero [41]. Pigmentation and scaling were reported with methenamine and pigmentation alone with glutaraldehyde in the study by Phadke *et al.* [42]. All of 12 patients treating palms with 20% aluminum chloride reported dryness of the skin and 4/12 reported stinging [44].

### Comments/implications for clinical practice

There is insufficient evidence to recommend topical treatments for palmar hyperhidrosis, and further RCTs are required. There is limited evidence of benefit from topical 5% methenamine.

## Botulinum toxin A

### Benefits

There are three trials that evaluated BTX-A for palmar hyperhidrosis [45–47]. In a double-blind RCT, 19 subjects were treated with 100 U BTX-A (Botox) to each palm, with each patient acting as their own control [47]. All patients reported that the treatment was successful compared with 12% for placebo at 29-day follow-up.

Saadia *et al.* compared 50 U versus 100 U BTX-A (Botox) to each palm of 24 subjects, where 12 were nonrandomized and 12 randomized to the different treatment groups [46]. The percentage of the palmar surface that was sweating changed from  $76 \pm 19\%$  in the 50 U group and  $59 \pm 34\%$  in the 100 U group to  $22 \pm 29\%$  and  $11 \pm 14\%$  respectively within 1 month post-injection. The effect remained significant at 6 months in the 50 U group and 5 months in the 100 U group.

In a small double-blind RCT, 120 U BTX-A (Dysport) was injected into one palm of 11 patients, with saline injected into the contralateral palm. Sweating was reduced by 31% as assessed through ninhydrin testing (95% confidence interval, 20–40%) at 13 weeks in the BTX-A treated palm, with no statistically significant reduction in the placebo palm. Subjective patient-reported outcomes paralleled these results.

A small ( $n = 8$ ) RCT used a conversion factor of 1:4 to compare the efficacy of Botox and Dysport and found comparable results. They reported a 72% and 75% subjective reduction in sweating at 3 months and a mean duration of effect of 18 weeks and 17 weeks with Botox and Dysport respectively (range 8–32 weeks for either preparation) [48]. In contrast, a non-blinded study ( $n = 36$ ) concluded that the conversion factor between Dysport and Botox was closer to 1–1.5:1 [49].

There is further evidence of efficacy in treating palmar hyperhidrosis from case series for both Botox 50 U ( $n = 23$ ) and 230 U Dysport ( $n = 21$ ) [50,51]. Anhidrosis lasted 7 months (mean) with Botox and 11 weeks (median) with Dysport.

### Harms

BTX-A injections into the palms are painful, necessitating local or regional anesthesia [47,52]. Seventy-seven percent of patients in the 100 U BTX-A (Botox) group and 45% of patients receiving 50 U BTX-A reported hand/finger weakness. Subjective weakness lasted up to 22 days, but objective weakness (as assessed by a

dynamometer) persisted until 6-month follow-up. Four of 19 patients reported adverse effects with 100 U Botox in the study by Lowe *et al.*, including thumb/finger weakness, tingling/numbness, and pain [47]. Three of 11 reported hand weakness lasting 2–5 weeks following Dysport injections [45]. Weakness of hand muscles was also reported in the study by Schnider *et al.* [51]. There were no reports of CH.

### Comments/implications for clinical practice

Based on relatively small studies, BTX-A appears effective in treating palmar hyperhidrosis. Injections are painful and local or regional anesthesia is required. There is considerable heterogeneity in studies in terms of doses, duration of follow-up, and the number of injection sites used. Transient weakness appears to be the commonest adverse event. There is at present insufficient evidence to recommend any one BTX-A preparation.

## Oral anticholinergics

### Benefits

Evidence for anticholinergic drugs is based on case series only. In a study by Castells Rodellas *et al.*, 6/12 patients with palmar or plantar hyperhidrosis responded to bornaprine after 1 week [53]. Methentelium bromide was found to reduce sweating by 24–80% in a small study of four patients [54]. In contrast, one RCT found no benefit with methentelium bromide compared with placebo [29].

### Harms

Oral anticholinergics can be associated with systemic adverse effects (e.g., dizziness, dry mouth, and eyes). One of 10 patients in the case series by Castells Rodellas *et al.* had to stop bornaprine due to anticholinergic adverse effects [53].

### Comments/implications for clinical practice

There is at present no good evidence to support the use of oral anticholinergics in treating palmar hyperhidrosis.

## Iontophoresis

### Benefits

In an RCT by Stolman *et al.*, one hand was treated with iontophoresis with the other hand acting as a control. A reduction in sweating was noted in 15/18 subjects as assessed through gravimetry [55]. A small RCT treated one hand with iontophoresis and the other with placebo and demonstrated an 81% reduction in sweating in 6/11 subjects with repeated fortnightly treatment [56]. Phadke *et al.* reported “good” or “excellent” results in 11/20 subjects after 4 weeks of iontophoresis in a non-blinded RCT [42]. Aguilar-Ferrández *et al.* randomized 96 subjects to receive iontophoresis, relaxation exercises, or both. Gravimetry and starch–iodine testing showed a reduced level of sweating in those receiving iontophoresis or iontophoresis plus relaxation exercises (no numerical data provided), when compared with relaxation exercises alone. In both of these groups a significant reduction in anxiety scores was noted [57].

Akins *et al.* evaluated the effects of a portable iontophoresis device suitable for home use in 10 patients with palmar hyperhidrosis [31]. The mean area of sweating in the treated palm reduced from 9.71 to 2.26 square inches, whilst there was no significant change in the control palm. Hölzle and Alberti reported a reduction of sweating in 7/12 subjects using the same iontophoresis device [58].

Na *et al.* reported that 9/10 patients were satisfied with a dry type of iontophoresis device. Notably, histology showed disruption of eccrine glands only in the treated palms [59].

Though direct current (DC) is most commonly used, Reinauer *et al.* compared DC with alternating current (AC) and AC with DC-offset (AC/DC) in 25 subjects with palmo-plantar hyperhidrosis who were blinded to the type of current administered [60]. DC as well as AC/DC normalized palmar sweating after 11 sessions, whilst AC yielded no improvement.

### Harms

Stolman *et al.* reported vesiculation, erythema, and a tingling sensation in a minority of patients. They reported no cases of CH [55]. Dahl and Glent-Madsen reported bullae forming in 1/11 subjects [56]. Reinauer *et al.* reported mild discomfort/skin irritation with DC iontophoresis, but not with AC/DC iontophoresis. Local irritation and occasional staining of the palms was reported by Na *et al.* with dry current application [59].

### Comments/implications for clinical practice

There is some evidence, albeit from small studies, that iontophoresis is effective for treating palmar hyperhidrosis. Skin irritation, discomfort, and vesiculation/blistering have been reported. Further studies will need to establish the optimal dose/type of current, treatment duration, and frequency.

## Iontophoresis in combination with other treatments

### Benefits

In addition to lone current application, iontophoresis has been combined with other treatments.

Shen *et al.* compared iontophoresis alone and in combination with 20% aluminum chloride and 0.01% glycopyrrolate ( $n = 8$ ) and reported superiority of the latter regime [61]. Dolianitis *et al.* reported that iontophoresis with 0.05% glycopyrrolate is associated with longer remission (median 11 days) when compared with iontophoresis alone (median 3 days) [62]. Shimizu *et al.* compared iontophoresis alone or in combination with oral oxybutynin 4 mg/day ( $n = 19$ ) in a nonblinded RCT, but reported no significant differences between groups.

Kavanagh and Shams reported a double-blind RCT of eight patients where BTX-A (Botox) was delivered successfully to the palms using iontophoresis. Mean improvement in the BTX-A treated palm was 66% as assessed through gravimetry, with no improvement in the placebo side [63].

### Harms

Shen *et al.* reported one subject with mouth dryness, whilst some patients noted peeling or vesiculation after treatment [61]. AC iontophoresis with/without oxybutynin was well tolerated [64]. In the study of glycopyrrolate iontophoresis the only reported adverse effect was dryness/soreness of the mouth or throat, which appeared more severe in some patients when both palms, rather than one, were treated with glycopyrrolate [62].

### Comments/implications for clinical practice

Very limited data suggest iontophoresis combined with BTX-A or with glycopyrrolate and/or aluminum chloride might be superior to iontophoresis alone. However, further studies are required before such combinations can be recommended in clinical practice.

## Sympathectomy

### Benefits

A retrospective survey of 270 patients (total of 480 T1–T4 sympathectomies) reported an improvement in 98% of patients [65]. A larger retrospective study of 734 sympathectomies in 406 patients reported anhidrosis in 92% in those undergoing conventional (open) sympathectomy and 97% of those undergoing VATS [66].

Baumgartner *et al.* compared sympathectomy of the second and third costal heads (R2/R3) in 121 patients with palmo-plantar hyperhidrosis [67]. Forty-five percent of those in the R2 group and 41% of those in the R3 group were “moderately” or “very” satisfied with results at 1 year.

Yazbek *et al.* compared T2 with T3 sympathectomies ( $n = 60$ ). All but one patient in the trial reported complete resolution of their hyperhidrosis at 1 month and 6 months postsurgery [68]. Those who responded to treatment ( $n = 59$ ) were followed-up for a mean period of 20 months (range 12–34 months). The improvement in hyperhidrosis appeared to be sustained during long-term follow-up [69].

Yang *et al.* randomized 163 to undergo either T3 or T4 sympathectomy and reported a resolution of palmar hyperhidrosis in all cases [70]. Ishy *et al.* also compared T3 versus T4 sympathectomies in an RCT of 40 subjects. Sympathectomy reduced sweating as assessed by epidermal water loss; from 120 to 30 g/(m<sup>2</sup>h) and from 118 to 37 g/(m<sup>2</sup>h) in the T3 and T4 groups respectively at 1 year [11]. There were no statistically significant differences between the T3 and T4 groups.

### Harms

Herbst *et al.* reported CH in 67%, gustatory sweating in 51%, Horner's syndrome in 3%, and pneumothorax in 2% of survey responders [65]. Neumayer *et al.* reported CH in 68% and 56% (difference not significant) and gustatory sweating in 50% and 33% of subjects undergoing conventional and video-assisted sympathectomies [66].

There were no statistically significant differences in the incidence of CH when R2 and R3 sympathectomies were compared. No other adverse effects were reported. Sympathectomy failed in 4.1% and 4.2% cases in the R2 and R3 groups respectively. The incidence of CH of any severity was 75.5% (R2) and 58% (R3), though the difference between R2 and R3 was not statistically significant [67].

CH was reported in all patients post T2 sympathectomy and in all but one patients post T3 sympathectomy at 6 months. There was one case of Horner's syndrome in 60 subjects [68]. Long-term follow-up suggests CH persisted for a mean period of 20 months [69]. CH occurred in significantly more subjects who underwent T3 compared with T4 sympathectomies in the study by Ishy *et al.*, in 20/20 versus 15/20 patients respectively [11]. Yang *et al.* report the same incidence of CH with T3 and T4 sympathectomies, but with a significantly larger number with more severe CH in the T3 group (mean follow-up 13.8 months) [70].

### Comments/implications for clinical practice

There is evidence for sympathectomies being effective for treating palmar hyperhidrosis. However, it is not clear which level is most effective and associated with fewest adverse effects. Retrospective data suggest comparable efficacy for conventional and video-assisted sympathectomies, but with a lower incidence of gustatory hyperhidrosis in the latter. Adverse events, in particular compensatory and gustatory sweating, are common and can be permanent. Sympathectomies should therefore not be considered a first line therapy.

### Key points

- Limited data suggest 10–30% aluminum chloride is effective, but there is a trade-off between efficacy and adverse effects (commonly skin irritation).
- RCT evidence suggests that botulinum toxin A is effective in focal hyperhidrosis. There are several commercial preparations available but it is unclear how they compare unit-per-unit in terms of efficacy, safety, and treatment duration. Adverse effects include pain on injection and compensatory hyperhidrosis (CH).
- There is limited evidence for the efficacy of oral anticholinergic drugs in axillary hyperhidrosis, but not for palmar hyperhidrosis. Their use is associated with anticholinergic adverse effects.
- Iontophoresis may be effective for palmar hyperhidrosis, though its efficacy in axillary hyperhidrosis is questionable. Local irritation is common.
- There is little evidence at present to support surgical removal of sweat glands, or the use of curettage, liposuction, microwave devices, or lasers in treating hyperhidrosis.
- There is evidence for efficacy of sympathectomy for palmar and to a lesser degree axillary hyperhidrosis. Adverse effects (notably CH and gustatory sweating) are common and may be permanent. For this reason, sympathectomies should only be considered in severe cases refractory to other treatments.

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## Appendix 59A: search strategies

### Central (Cochrane Library) search strategy

- #1 MeSH descriptor Hyperhidrosis explode all trees
- #2 MeSH descriptor Sweating, Gustatory explode all trees
- #3 MeSH descriptor Sweating explode all trees
- #4 (hyperhidrosis or hyperhidrosis or hyperperspiration)
- #5 “frey\* syndrome”
- #6 (perspir\* or sweat\*) and (idiopathic or excessive)
- #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

### Medline (OVID) search strategy

1. hyperhidrosis.ti,ab.
2. hyperhidrosis.ti,ab.
3. hyperperspiration.ti,ab.
4. perspir\$.ti,ab.
5. sweat\$.ti,ab.
6. 4 or 5
7. idiopathic.ti,ab.
8. excessive.ti,ab.
9. 7 or 8
10. 6 and 9
11. frey\$ syndrome.ti,ab.
12. exp Sweating, Gustatory/
13. exp Hyperhidrosis/
14. Sweating/
15. 1 or 2 or 3 or 10 or 11 or 12 or 13 or 14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized.ab.

19. placebo.ab.
20. clinical trials as topic.sh.
21. randomly.ab.
22. trial.ti.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. (animals not (human and animals)).sh.
25. 23 not 24
26. 15 and 25

### Embase (OVID) search strategy

1. hyperhidrosis.ti,ab.
2. hyperhidrosis.ti,ab.
3. hyperperspiration.ti,ab.
4. perspir\$.ti,ab.
5. sweat\$.ti,ab.
6. \*sweating/
7. 4 or 5 or 6
8. idiopathic.ti,ab.
9. excessive.ti,ab.
10. 8 or 9
11. 7 and 10
12. \*Frey syndrome/
13. frey\$ syndrome.ti,ab.
14. \*hyperhidrosis/
15. \*sweat gland disease/
16. 1 or 2 or 3 or 11 or 12 or 13 or 14 or 15
17. random\$.mp.
18. factorial\$.mp.
19. (crossover\$ or cross-over\$).mp.
20. placebo\$.mp. or PLACEBO/
21. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
22. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
23. (assign\$ or allocat\$).mp.
24. volunteer\$.mp. or VOLUNTEER/
25. Crossover Procedure/
26. Double Blind Procedure/
27. Randomized Controlled Trial/
28. Single Blind Procedure/
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 16 and 29

### Liliacs search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and hyperhidrosis or hyperhidrosis or sweat\$ or hyperperspiration or frey\$ or perspir\$ [Words]

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**Background**

Minimally invasive cosmetic procedures are increasingly popular treatments for rejuvenation. Dermal fillers are used to improve contours and wrinkles which occur as a result of volume loss and repetitive muscle contraction. A wide variety of fillers is available, ranging from temporary agents such as hyaluronic acid (HA), to permanent agents such as polyacrylamide hydrogel. Temporary fillers are often preferred owing to a more favorable side-effect profile. Furthermore, facial ageing is a dynamic process; therefore, use of temporary fillers allows for adjustment of treatments over time.

**Etiology**

Facial ageing is a complex process due to a combination of changes occurring at all tissue levels from the epidermis to the facial skeleton. Cutaneous ageing occurs as a result of extrinsic factors, primarily ultraviolet radiation, superimposed on chronologic or intrinsic skin ageing. The epidermis may be thinned, and an increase in the activity of proteolytic enzymes results in reduced collagen expression. Repeated exposure to ultraviolet radiation leads to deposition of abnormal elastotic material in the dermis. There is atrophy of subcutaneous tissues; the diminution and flattening of discrete facial fat pads with subsequent malposition results in phenotypic changes characteristic of the older face; for example, flattening of the mid face and jowl formation [1]. Dynamic lines and wrinkles associated with facial expression can with time become permanent creases present at rest. Changes in the facial skeleton including the orbital aperture and mandible may result in altered prominence of periorbital fat pads, deepening of sulci, and decreased chin projection [2,3].

**Aims of treatment**

The aim of treatment with dermal fillers is to replace volume to produce a more youthful appearance.

**Relevant outcomes**

The majority of studies are focused on treatment of nasolabial folds (NLFs) and assess improvements in the five-point wrinkle severity rating scale (WSRS, a scale of 1–5, where 1 indicates no visible fold

and 5 indicates extremely deep and long folds) and the global aesthetic improvement scale (GAIS, where the improvement is rated on a five-point scale: 0 indicates worse and 4 indicates very much improved) [4]. The duration of effect is also an important consideration.

**Methods of literature search**

The following databases were searched using the term “dermal filler” or “dermal fillers”: The Cochrane Library, PubMed, OVID, and the Clinical Trials Database. All randomized studies of dermal fillers used for the purposes of facial rejuvenation were included. Trials of dermal fillers for the treatment of HIV-associated lipodystrophy or skin diseases such as acne were excluded.

**Questions****Which fillers are effective in treatment of nasolabial folds?**

The vast majority of randomized studies have compared the effects of two or more different types of fillers in the treatment of NLFs. HA-based products are the most studied, with a number of trials demonstrating significant improvement in NLFs following treatment. Most studies received industry funding.

**Hyaluronic acid**

HA is a glycosaminoglycan found within the dermis. A number of HA-based formulations are available for rejuvenation. Nonanimal HA products are made from bacterial fermentation cultures. Several double-blind (subject and evaluator blind) studies have shown that some crosslinked HA fillers (e.g., Emervel Classic, Emervel Deep, Restylane, Restylane Perlane, Teosyal Deep) and to a lesser extent non-cross-linked HAs (Mesoglow, IAL-System) are effective in the treatment of NLFs, with the duration of treatment efficacy for cross-linked products generally assessed up to 6 months [5–9]. A single-blind randomized study of 77 individuals studied two different nonanimal stabilized HA (NASHA) products with different physicochemical qualities, including degree of cross-linking (Perlane and Juvederm ULTRA PLUS) over 12 months [10]. Although both

products resulted in similar improvements in WSRS up to 3 months posttreatment, at 6, 9, and 12 months the proportion of patients with clinically relevant improvement (one point difference in the WSRS) was greater in the Juvederm ULTRA PLUS treated side. The authors hypothesized that the greater degree of cross-linking and dense network of HA polymers increased the longevity of the product. A small randomized split-face study comparing three different HA fillers also reported benefits lasting up to the final 12-month follow-up [11].

The majority of patients studied have been Caucasian; however, one study has shown that NASHA gels are safe and effective in the treatment of NLFs in 150 individuals with Fitzpatrick skin types IV to VI, although pigmentary disturbance was reported in 6–9% of patients depending on the type of NASHA used [12]. A number of randomized controlled trials (RCTs) have compared NASHA filler containing lidocaine with the same product without lidocaine [13–16]. All revealed significantly lower reported pain scores with the lidocaine-containing product (varying from time of injection to 120 mins post injection), and the majority of patients preferred the lidocaine-containing products; efficacy and safety were not affected.

Nonanimal stabilized HA fillers have been compared with other HA products. A randomized study of 15 patients comparing NASHA (Restylane) with an avian-derived HA (Hylan B gel) in a split-face design showed that, although both products led to improvement in NLFs as assessed by physician- and patient-reported WSRS, the effects of NASHA were more pronounced and more long lived (improvement maintained at final 6-month assessment, compared with 3 months for avian-sourced HA) [17]. More recently, a randomized evaluator blinded study of 140 subjects reported equivalent safety and efficacy of a novel divinyl sulfone cross-linked HA (Prevelle lift) compared with NASHA (Restylane) in the treatment of NLFs [18].

### Drawbacks

Adverse events reported include bruising, redness, swelling, pain, itching, and nodules lasting several days [6,11,17,19]. In one study redness lasted beyond 2 weeks in an unspecified number of patients [16], whilst in a separate study of 248 subjects treated with NASHA, six developed masses or nodules, two of which required treatment [5].

Please note that in contrast to all other fillers, in case of overcorrection and adverse reactions to HAs an antidote (hyaluronidase) is available.

### Collagen

The most-studied collagen fillers are bovine in origin, although porcine and human collagen products are or have also been available. Owing to the immunogenicity of bovine collagen, patients must have hypersensitivity testing prior to filler injection. A split-face randomized trial of 137 patients treated with bovine collagen (Zyplast) and NASHA (Restylane) in NLFs reported significantly greater improvement in the WSRS and GAIS at 2, 4, and 6 months post injection in the NASHA-treated side (although both resulted in improvement compared with baseline). Delayed-onset reactions (mainly redness) occurred in 10 NASHA and 11 bovine collagen-treated sites, but none were considered hypersensitivity reactions and all resolved spontaneously [4]. Similar findings were reported in four subsequent randomized trials, again using split-face designs, to compare bovine collagen with different HA fillers (number of subjects ranging from 69 to 439) [20–23]. The effects of the HA fillers were longer lasting (up to 12 months), and adverse events

were similar (mainly short-lived injection-site reactions). In one of the studies the incidence of local injection-site reactions with bovine collagen was 30.9% compared with 17.6% with NASHA [22].

More recently, porcine collagen has been studied as an injectable filler. A small randomized split-face study of 12 patients injected with bovine collagen (Zyplast) and porcine collagen (Evolve) into NLFs found that, although both treatments improved NLFs, the effects of porcine collagen persisted for longer [24]. Comparison of porcine collagen (Evolve) with NASHA (Restylane) in an evaluator and subject blind RCT of 149 patients revealed that both treatments led to significant improvement in NLFs with no differences between the two fillers [25]. A follow-up study showed that at least some improvement (0.5-point improvement in a modified WSRS, ranging from 0 to 4) was still evident in the majority of patients (76.5%) treated with porcine collagen at 12 months [26]. Six months after injection of porcine collagen, local injection-site reactions (including induration) were present in 3.4% of subjects, compared with 0.7% with NASHA.

Please note that in most parts of the world collagens are not available anymore.

### Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a biodegradable polymer that has been shown to be effective in the correction of NLFs. A randomized evaluator blind study of 233 patients treated with either PLLA or human collagen to NLFs (up to four treatments given over 3-week intervals to achieve optimum correction, using a six-point WSRS) demonstrated a significant improvement in NLFs with both treatments. At 3-month follow-up no significant difference compared with baseline was apparent in the collagen group. In contrast, PLLA resulted in significant reduction in NLF severity score up to 25 months [27]. However, the correction was modest and less than that seen in HA filler studies. Injection-site reactions occurred more commonly in the collagen group, although a higher incidence of application-site papules was noted in the PLLA group.

Please note that the correction achieved with PLLA was less than for HAs and that, in contrast to the HAs, no antidote exists for overcorrection or in case of adverse events.

### Calcium hydroxylapatite

Calcium hydroxylapatite (CaHA) is a mineral complex that is used as a temporary dermal filler for facial rejuvenation. A randomized split-face evaluator blind study of CaHA (Radiesse) versus human collagen in the treatment of 117 patients showed that significantly more NLFs treated with CaHA had improved in terms of wrinkle severity scores at 3 months (87% improved compared with 27% of collagen treated) [28]. The same effect was observed at 6-month follow-up. Swelling and bruising were more common in the CaHA-treated side. Two randomized split-face studies comparing CaHA with HA products showed different results. The larger study did not show a difference in the WSRS, whereas the smaller study favored in the WSRS the CaHA-treated site [29,30]. Patient preference and satisfaction with treatment favored CaHA (however, one has to note that neither study was double blind; therefore, a bias might favor the treatment under study), and no serious adverse events were reported for either treatment. Two small randomized split-face studies have compared CaHA with and without lidocaine for the treatment of NLFs [31,32]. One double-blind study of 16 patients found an improvement in pain scores with no difference in efficacy up to 6 months posttreatment [31]. A second randomized study of

50 patients showed improvement in pain scores both at the time of injection and up to 1 h post injection. This study was limited by the lack of evaluator blinding and a short follow-up period of 1 month [32].

Please note that, in contrast to the HAs, no antidote exists for overcorrection or in case of adverse events.

### Autologous fibroblast therapy

A randomized placebo-controlled study of 372 patients has shown that autologous fibroblast therapy resulted in greater improvement in NLF wrinkles during the 6-month study period when compared with placebo injection, although there was a notable placebo effect [33]. Adverse events were generally injection related: redness occurred more commonly following fibroblast injection, whereas bruising occurred more commonly after placebo. Two individuals treated with fibroblast injections developed papules and a further two developed hyperpigmentation lasting beyond 2 weeks. Without an active comparator arm the results are difficult to interpret.

Please note that this is not a commonly used intervention.

### Polymethylmethacrylate microspheres and polyacrylamide hydrogel

Polymethylmethacrylate microspheres suspended in bovine collagen, known as Artecoll or Artefill, can be used as permanent injectable filler. One double-blind randomized study of 251 patients compared Artecoll with bovine collagen (Zyderm/Zyplast) in the treatment of glabellar lines, upper lip lines, NLFs, and marionette lines [34]. At 6-month follow-up the improvements in observer-rated facial fold severity scores across facial areas overall were significantly greater in the Artecoll group. The effects were persistent at 12-month follow-up, although data were only available for the Artecoll group. The numbers of adverse events were similar in both groups and were mainly injection-site reactions, although more patients in the Artecoll group had lumpiness lasting more than 1 month at the injection site (eight compared with four).

Injectable filler containing polyacrylamide hydrogel has been compared with NASHA in the treatment of NLFs in a randomized double-blind study of 315 patients [35]. The treatments were equivalent in terms of improvement in WSRS at 12 months. The majority of adverse events were injection-site reactions; more than 85% of which resolved in less than 7 days. One patient treated with polyacrylamide hydrogel developed an infection requiring antibiotics and filler removal. Further studies are required to assess the long-term safety of the filler.

There have been a number of reports of granulomatous reactions occurring months to years post injection of these permanent fillers (0.6% occurrence rate with polymethylmethacrylate microspheres). Treatments include intralesional steroid injection or surgical removal of the implant [36].

Please note that permanent fillers should always be scrutinized for long-term safety.

### Which fillers are effective in the treatment of glabellar lines?

One small randomized study of 38 female patients compared NASHA alone with NASHA and botulinum toxin in the treatment of moderate to severe glabellar lines [37]. A significantly higher proportion of subjects receiving the combined treatment achieved improvements in wrinkle scores from week 0 to week 32. The rates of adverse events were similar, although one patient in the NASHA

group developed what was presumed to be a delayed reaction to NASHA that responded to intralesional steroid injection.

### Which fillers are effective in cheek augmentation?

One RCT of 107 patients has studied the effect of CaHA in cheek augmentation [38]. Patients receiving treatment were compared with an untreated control group at 3 months. The untreated group then went on to have treatment at 3 months. The treated group had greater GAIS at 3 months, and 77.9% of patients were satisfied or extremely satisfied with the treatment. Injection-site reactions were common, with 6.5% of patients reporting lumps and 1.9% reporting nodules (duration not stated). Again, this trial is hampered by a missing active comparator.

### Which fillers are effective in lip augmentation and rejuvenation of the lower face?

A double-blind randomized comparison of porcine collagen, bovine collagen, or HA (Perlane) to treat wrinkles in the upper lip of 79 patients demonstrated modest increases in lip volume post injection [39]. Herpes zoster was the most common adverse event in all groups. Larger studies are necessary to determine the safety and efficacy of fillers in lip augmentation.

One RCT has reported the effect of HA with or without botulinum toxin for lower facial rejuvenation [40,41]. Ninety subjects were enrolled; although only 73 attended the 24-week follow-up. Subjects receiving combination treatment in general had greater improvements in investigator assessments with a longer duration of response. Adverse events were more noticeable in the botulinum-toxin-treated group.

HA has been shown to be effective in lip augmentation in a randomized evaluator-blind trial of 180 patients, although the comparison group had no treatment [42]. Injection-site reactions were mainly mild in severity and lasted 5–10 days after injection.

## Summary

In contrast to other interventions in esthetic medicine, at least some randomized clinical trials exist investigating a number of injectable fillers available in the marketplace. However, not every trial is a good one, and the common indications for use of such fillers now far outstrip the available randomized, blinded clinical evidence. The users should scrutinize the evidence carefully in several instances: (1) Small trials – results are more likely to be due to chance. (2) Single-blinded trials where one investigator is blinded; for example, the WSRS results may be reliable but subjective patient-centered results may be biased to the new treatment. (3) Trials with a weak comparator – bovine collagen was nearly always inferior to the new fillers investigated (one of the reasons they are no longer marketed in Europe and the USA); therefore, it is not surprising if a filler is superior to bovine collagen. (4) Trials with no comparator – a study with absence of a comparator might mean that the study designers are not sure of the effect of their product compared with a standard HA; for example, the effect may at best be equal to or even inferior to that of a standard HA. (5) Last but not least, permanent fillers. This is a specific group. Attention should be paid here not only to short-term safety, but also to long-term safety.

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# Reducing mimic wrinkles and folds with botulinum toxin A

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## Background

Mimetic muscles create facial expressions. Because these are usually attached to the dermis, activation can result in development of temporary cutaneous wrinkles and folds which convey emotion. Over time and with repeated muscular activity, temporary lines and wrinkles in the skin may become permanent and persist at rest. Wrinkles and folds are significantly associated with aging [1]; therefore, modification of these will be inexorably linked with facial rejuvenation.

The most basic intervention to decrease mimetic wrinkles and folds is treatment with botulinum toxin type A (BoNT-A). BoNT-A binds uniquely at the acetylcholine-triggered neuromuscular synapse temporarily blocking muscular activity (de Maio and Rzany, 2007). There are several BoNT-A preparations on the market. This chapter will focus on the three brands available in Europe and North America (Table 61.1), although other preparations are available worldwide; for example, Neuronox [2].

## Aim of treatment

The aim of treatment is to decrease muscular activity and thus decrease the severity of wrinkles and folds.

## Outcome criteria

Efficacy of treatment is measured by clinical severity scales. These four- to six-point scales range from “no wrinkles” up to “extreme wrinkles.” The clinical scales can be used by physicians as well as patients. They have been used with life patients as well as photographs. In clinical trials, physicians and patients are usually blinded. If for some reason the treating physician cannot be blinded, then to increase the level of blinding a blinded evaluator can be used. Reproducibility of these scales has been shown to be good to excellent [3,4]. In most BoNT-A studies, a four-point score is used. Treatment success might be defined as either the proportion of patients with mild or no wrinkles or alternatively as at least a one point or two point difference in the wrinkle score. Treatment success of either outcome measurement is usually associated with high patient satisfaction despite which main objective outcome criterion was used [5]

## Relevant clinical questions

Since the early 1990s [6] BoNT-A has been used for a multitude of indications, mostly focusing on muscle-induced wrinkles and folds ranging from the glabella to the platysmal bands. Based on these different indications, as well as the desired wanted and unwanted outcomes, there are a multitude of possible questions. Some of these questions will focus on indications (e.g., the glabella, the forehead, crow’s feet), mode of treatment (e.g., distribution of injection points, dilution used), as well as general aims of treatment. Here, we can only provide a brief overview, focusing on four relevant clinical questions:

- 1 What is the optimal dosage for the muscles (m. corrugatores, m. procerus) inducing vertical and/or horizontal wrinkles/folds of the glabella?
- 2 What is the optimal dosage for the muscle (m. frontalis) inducing horizontal wrinkles/folds of the forehead?
- 3 What is the evidence for reducing injection pain when administering BoNT-A?
- 4 What is the evidence that BoNT-A may be used for the prevention of wrinkles and folds?

## Methods

Criteria for inclusion were unsystematic searches in the Cochrane library as well as Embase and Medline, with a focus on systematic reviews and randomized controlled clinical trials (RCTs) up to December 2012. Search terms were botulinum toxin, the drug names,<sup>1</sup> glabella, forehead, crow’s feet, pain, preserved saline, as well as clinical trial and randomised/randomized. Small RCTs and RCTs with inappropriate study designs were excluded. Good examples of inappropriate study designs are the studies from Prager and Rappl. [7] and Moers-Carpi *et al.* [8], where two dosages in two

<sup>1</sup>The different toxin preparations can be found under different names in the data banks, ranging from their trade names to designed names that are preferred by the US Food and Drug Administration (FDA). For example, Botox (original trade name, used for medical as well as esthetic indications – sometimes with the addition of “cosmetic” – is also called Vistabel/Vistabex/Vista (trade name for esthetic indications in some countries) as well as onabotulinumtoxin (the designed name preferred by the FDA) (see also Table 61.1).

different products were compared in a two arm study. An appropriate study design would have required here a four-arm study. Excluded were also a couple of forehead studies as they focused more on the comparison of different BoNT-A preparations than on the optimal dosage for this indication [9,10].

## Clinical questions

### What is the evidence for the optimal dosage for treating vertical and/or horizontal wrinkles and folds of the glabella?

Glabella wrinkles and folds are induced basically by two muscle groups: the procerus (leading to horizontal lines) and the corrugators (leading to vertical lines). In clinical trials, usually five to seven injection points are delivered.

### Randomized controlled trials and meta-analyses

There is one company-sponsored meta-analysis available [11]. In addition, several good controlled trials can be found. The trials will be discussed for each brand separately.

**Table 61.1** Botulinum toxin A preparations available in Europe and the USA.

Trade name	Units <sup>a</sup> per vial	US acronym	Company
Azzalure <sup>b</sup> /Dysport	125 <sup>b</sup> /300 or 500	AbobotulinumtoxinA (Abo-BoNT-A)	IPSEN
Bocouture/Xeomin	50/100	IncobotulinumtoxinA (Inco-BoNT-A)	Merz
Vistabel, Vistabex, Vista/Botox	50/100	OnabotulinumtoxinA (Ona-BoNT-A)	Allergan

<sup>a</sup>1 U of Azzalure/Dysport is approximately equivalent to 2.5 U of Vistabel/Botox. 1 U of Bocouture/Xeomin is approximately equivalent to 1 U of Vistabel/Botox.

<sup>b</sup>Distributed by Galderma.

### Ona-BoNT-A (Botox or Botox Cosmetic or, for example, Vistabel)

There are several trials focusing on the optimal dosage for Ona-BoNT-A in the glabella area (Tables 61.2 and 61.3).

**Five injection-point studies** The standard dose used is 20 U Ona-BoNT-A distributed in five injection points. In the first large placebo-controlled trial, patients with moderate to severe glabellar lines at maximum frown received intramuscular injections of 20 U Ona-BoNT-A or placebo into five glabellar sites. A total of 264 patients were enrolled (203 treated with Ona-BoNT-A, 61 with placebo). There was a significantly greater reduction in glabellar line severity with Ona-BoNT-A than with placebo (all measures, every follow-up visit;  $P < 0.02$ ). The effect was maintained for many patients throughout 120 days, the duration of the study [12]. Similar studies were conducted in Asia [13,14]. The Japanese study was a three-arm study additionally investigating an 10 U Ona-BoNT-A arm [13]. Study designs and results were comparable; therefore, the meta-analysis was performed focusing on the duration of the effect (Table 61.2).

**Seven injection-point studies** The same authors investigated in a double-blind, randomized clinical trial the efficacy, safety, and duration of the effect of four different doses of Ona-BoNT type A in the treatment of glabellar rhytids in females. Eighty female subjects with moderate to severe wrinkles at maximum frown entered the study. Patients were randomly administered 10, 20, 30, or 40 U Ona-BoNT-A in seven injection points. Objectively, 10 U of Ona-BoNT type A was significantly less effective than 20, 30, or 40 U. The relapse rate at 4 months was significantly higher in the 10 U group (83%) versus 40, 30, or 20 U (28%, 30%, and 33% respectively). The authors concluded that 20–40 U Ona-BoNT-A were significantly more effective at reducing glabellar lines than 10 U [15].

**Table 61.2** RCTs focusing on the BoNT-A dosage (here the Botox family of products) for the glabella using five injection points.

Author Year Country	Study type No. of patients % female Dose Injection points	Outcome criteria	Results	Comment
Carruthers <i>et al.</i> [12] 2002 USA and Canada	RCT 203 Ona-BoNTA and 61 placebo 85.2% and 77% respectively 20U or placebo 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: placebo, 1.6%; 20U Botox, 83.7%	
Carruthers <i>et al.</i> [17] <sup>a</sup> 2003 USA and Canada	RCT 202 Ona-BoNTA and 71 placebo 79.7% and 83.1% respectively 20U or placebo 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: placebo, 7%; 20U Botox, 76.7%	Placebo rate estimated from graph may be a bit lower
Wu <i>et al.</i> [14] <sup>a</sup> 2010 China	RCT 170 Ona-BoNTA and 57 placebo 85.9% 20U or placebo 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: 20U Botox 94.1%; placebo, 3.5%	
Harii and Kawashima [13] <sup>a</sup> 2008 Japan	RCT 142 patients 90% 10 or 20U Ona-BoNT-A or placebo 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At 4 weeks: 10U Botox 86.4%; 20U Botox 88.6%; placebo 0%	Both doses are efficient

<sup>a</sup>Evaluated in a meta-analysis.

**Table 61.3** RCTs focusing on the BoNT-A dosage (here the Botox family of products) for the glabella using seven injection points.

Author Year Country	Study type No. of patients % female Dose Injection points	Outcome criteria	Results	Comment
Carruthers and Carruthers [16] <sup>a</sup> 2005 Canada	RCT 80 Ona-BoNT-A 0% 20, 40, 60, or 80 U Ona-BoNTA 7	Physician assessment Responder: grade 0 or 1 at maximum frown	At 1 month: 20 U Botox, 65%; 40 U Botox, 90 %; 60 U Botox, 95%; 80 U Botox, 100%	All-male study
Carruthers <i>et al.</i> [15] 2005 Canada	RCT 80 Ona-BoNT-A 100% 10, 20, 30, or 40 U Ona-BoNTA 7	Physician assessment Responder: grade 0 or 1 at maximum frown	At 4 weeks: 10 U Botox, 68%; 20 U Botox, 78%; 30 U Botox, 98%; 40 U Botox, 100%	All-female study 10, 20, and 30

<sup>a</sup>Estimated from the graphs.

A similar study in male patients was published the same year. In this comparable study, 80 men were randomized to receive a total dose of either 20, 40, 60, or 80 U of Ona-BoNT-A distributed in seven points in the glabella and lower forehead area. The 40, 60, and 80 U doses of Ona-BoNT type A were consistently more effective in reducing glabellar lines than the 20 U dosage (duration, peak response rate, improvement from baseline). There was a dose-dependent increase in both the response rate at maximum frown and the duration of effect assessed by the trained observer. The authors concluded that male participants with glabellar rhytids benefit from starting doses of at least 40 U of Ona-BoNT-A [16] (Table 61.3). With seven injection points the recommended dosages are higher than for the five injection point studies.

#### **Abo-BoNT-A (Dysport or Azzalure)**

Up to now there has been no meta-analysis published. However, there is a clinical overview which summarizes the relevant clinical data for Abo-BoNT-A [5]. In this overview there are a total of 11 clinical studies evaluated, the majority being RCTs. For this review we focus on RCTs only.

So far there are four more-or-less comparable trials published focusing on the optimal dosage for the glabella [18–21]. The baseline is a dose ranging study from Ascher *et al.* [18] comparing 25, 50, and 75 sU Abo-BoNT-A compared with placebo. A total of 119 patients with moderate to severe glabellar lines at rest were treated. The dose was distributed over five intramuscular glabellar sites forming a bird-shaped pattern. Outcome measures included evaluations of glabellar lines by independent experts from blinded standardized photographs at rest 1 month after treatment, physician evaluations, and patient assessments during a 6-month period. A significant efficacy was reported for the three Abo-BoNT-A groups for at least 3 months after injection (at least  $P < 0.015$ ). Investigator and patient evaluations suggested that 50 sU was the optimal dosage [18]. These results are supported by the US study from Monheit *et al.* [19] and Brandt *et al.* [21].

The most interesting study is that from Kane *et al.* [22] looking at variable dosages. In this study Abo-BoNT-A was administered in a total volume of 0.4–0.6 mL for women (50, 60, or 70 sU) and 0.5–0.7 mL for men (60, 70, or 80 sU), based on procerus/corrugator muscle mass (e.g., the activity of the muscles). At day 30, 85% and 87% of Abo-BoNT-A-treated patients were responders as assessed by blinded evaluator and patient self-evaluation, respectively, compared with 3% and 5% of placebo-treated patients, respectively

( $P < 0.001$ ). This study shows that an individualized treatment will lead to an increased efficacy (Table 61.4).

#### **Inco-BoNT-A (Xeomin or Bocouture)**

For Inco-BoNT-A (Xeomin) no placebo-controlled studies have been published so far. There is only one study that does not see a difference between 24 U of Inco-BoNT-A (Xeomin) and Ona-BoNT-A (Botox) for the glabella (Table 61.5).

#### **Summary**

Based on these studies (with an overwhelming female study population) 20 U Ona-BoNT-A (Botox) and 50 sU Abo-BoNT-A (Dysport) seems to be the optimal dosage when treating the glabella only. This corresponds to a 1:2.5 ratio between both products, taken on the existing data alone. When treating the glabella and forehead with two additional points the optimal dosage seems to be higher. Using a seven-point injection scheme Carruthers and Carruthers [16] suggested 40 U Botox to be the optimal dosage for the treatment in men.

For Inco-BoNT-A (Xeomin) no placebo-controlled studies have been published so far. Therefore it can only be assumed that the optimal dosage corresponds to the dosage of Ona-BoNT-A.

It is useful to note that the studies discussed here may comprise quite different patient populations; therefore, simple informal indirect comparison between the efficacy rates of the different products may be misleading. A real comparison would require a head-to-head trial.

Another confounding issue is the paucity of data for the esthetic use of BoNT-A in areas other than the glabella. The reluctance of regulatory agencies to accept clinical studies outside their jurisdiction is certainly a contributory factor. There would be significant clinical benefit for utilization of resource on other important applications of BoNT-A; for example, crow's feet and forehead wrinkles.

#### **What is the evidence for the optimal dosage for treating horizontal wrinkles and folds of the forehead?**

Besides the glabella, the wrinkles and folds of the forehead are the most frequently treated indications. These mostly horizontal wrinkles and folds are induced by one major muscle: the frontalis. This is the only elevator for the upper third of the face; therefore, over-treatment will inevitably lead to brow ptosis, which is associated



**Table 61.4** RCTs focusing on the BoNT-A dosage (here the Dysport/Azzalure product family) for the glabella. The dosage is given in Speywood units (sU).

Author Year Country	Study type No. of patients % female Dose Injection points	Outcome criteria	Results	Comment
Ascher <i>et al.</i> [18] 2004 France	RCT 119 95.8% 25–75 sU 5	Assessment at rest	44.8% in the BonNT-A (25 sU) and BonNT-A (50 sU) groups ( $P = 0.015$ ); 55.2% in the BTX-A (75 sU) group ( $P = 0.005$ ); and 6.7% in the placebo group	Assessment was done at rest. This makes the study difficult to compare
Rzany <i>et al.</i> [20] 2006 Germany	RCT 110 and 111 89.9% and 90.1% 30–50 sU 3 or 5 (the latter distributed in a U-shape pattern)	Assessment by experts based on photographs Responder: a reduction of at least 1 point between weeks 0 and 4	After 4 weeks, the proportions of responders were 86.1% vs 18.9% for 30 sU and 86.3% vs 7.9% for 50 sU	This was not a dose-finding study. Two different injection point distributions and dosages were compared with placebo
Monheit <i>et al.</i> [19] 2007 USA	RCT 373 83.9% 20–75 sU 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: Placebo, 9%? 20 sU, 68%? 50 sU, 79%? 75 sU, 84%?	Data not given in paper, the proportions are estimated from a PP from Gary Monheit. 50 sU Dysport were determined to be the optimal dosage
Brandt <i>et al.</i> [21] 2009 USA	RCT 158 85% 50 sU 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: 50 sU, 89%; placebo, 3.9%	
Kane <i>et al.</i> [22] 2009 USA	RCT 816 88% Variable dose (50, 60, or 70 sU) for women and (60, 70, or 80 sU) for men 5	Physician assessment Responder: grade 0 or 1 at maximum frown	At day 30: variable dosages sU 85% Placebo: 3% Median duration of effect: 109 days (blinded evaluator) vs 0 days for placebo	Very innovative study trying to individualize dosages based on muscle mass

**Table 61.5** RCTs focusing on the BoNT-A dosage (here the Xeomin/Bocouture product family) for the glabella.

Author Year Country	Study type No. of patients % female Dosage Injection points	Outcome criteria	Results	Comment
Sattler <i>et al.</i> [23] 2010 Germany, Austria, UK	RCT 381 Inco- or Ona-BoNT-A patients 100% 24U 5	Physician assessment Responder: 1 or more improvement of the 4-point FWS scale	At 4 weeks: 24U Xeomin (Inco-BoNT-A), 96.4%; 24U Botox (Ona-BoNT-A), 95.7%	This is the only published RCT so far. The results of the placebo-controlled trials have yet to be published

with a sad-looking appearance and considered to be an unsatisfactory outcome.

Two randomized controlled clinical trials were identified focusing on Ona-BoNT-A for the treatment of forehead lines [24,25]. The Keen trial (1994) was a very small, placebo-controlled trial that basically showed that Ona-BoNT-A was effective in reducing forehead wrinkles. The Carruthers trial was a three-arm dose-response trial that clearly showed an advantage of the two higher doses tested. Interestingly, the number of adverse events was not very different between the three arms. Brow ptosis was only observed in the two higher dosage groups, with 21% and 10%. Another trial was identified comparing in a split-face study Ona-BoNT-A and Abo-BoNT-A for three indications [26]. Not surprisingly, the highest efficacy of forehead wrinkle reduction correlated

with most marked reduction in brow elevation. Although no adverse events were reported in this study, a significant inability to lift the brow might be considered also as an adverse event (Table 61.6). This highlights the fact that balance and proportion of facial landmarks may be more important from an esthetic perspective than simply reduction in wrinkles and lines.

### Summary

The evidence for the treatment of the forehead lines is still insufficient. Only three RCTs for two of the three BoNT-A preparations were found. Further studies are needed for this indication to determine the optimal dosage, taking into account not only forehead wrinkle reduction, but also considering reduction in brow elevation for best cosmetic outcome.

**Table 61.6** Studies focusing on the treatment of forehead wrinkles with BoNT-A (different types).

Author Year Country	Study type No. of patients % female Injection points (IP) Dose Duration	Inclusion criteria	Outcome criteria	Results	Comment
Carruthers <i>et al.</i> [24] 2003 USA	RCT 59 100% 8 IP (4 forehead, 2 orbicularis oculi, 2 procerus) 16, 32 or 48U Botox (if only the forehead is considered: 8, 16 and 24U) (Ona-BoNT-A) 44 weeks	Moderate (2) to severe (3) horizontal forehead wrinkles	None (0) or mild (1) on the 4-point FWS	At 2 weeks response rates of 84%, 89%, and 95% at contraction. Higher dosages were associated with a significant trend showing increasing time to relapse	Besides the m. frontalis (elevator) two depressors (m. orbicularis oculi and m. procerus) were treated in this study
Keen <i>et al.</i> [25] 1994 USA	RCT 11 63% 9 IP forehead or 2 IP crow's feet 0.2 cm <sup>3</sup> of Ona-BoNT-A (10U) or placebo	None given	4-point FWS	Mean reduction of 1.3 injection points	Ona-BoNT-A was more effective than placebo
Michaels <i>et al.</i> [26] 2012	RCT 53 98% Three indications: forehead, glabella, and crow's feet Total dosage of 25U Botox (Ona-BoNT-A) or 62.5sU Dysport (Abo-BoNT-A) (with forehead dosages of 6U and 15sU respectively )	Not clear	FWS (from 0 to 3 with subgroups) and eyebrow height measurement	After 90 days 75% (Dysport) and 72% (Botox) of improvement respectively After 150 days 64% (Dysport) and 60% (Botox) of improvement respectively	No significant difference between Ona- and Abo-BoNT-A using a 1:2.5 ratio

**Table 61.7** RCTs focusing on the use of saline with a preservative.

Author Year Country	Study type Study design No of patients/locations	Outcome criteria	Results	Comment
Alam <i>et al.</i> [28] (III/B) 2002 USA	RCT Double blind Randomized Ona-BoNT-A diluted with 5 mL (benzyl alcohol: 9 mg/mL) vs standard saline <i>n</i> = 15 Multiple locations	Percentage of change of discomfort	15 (100%) patients reported less pain in the side of their face treated with the product reconstituted with preservative containing saline ( <i>P</i> = 0.001). Pain on the preservative-containing side was 54% less	Small trial
Sarifakioglu and Sarifakioglu [29] (III/B) 2005 Turkey	CT Single blinded Not randomized 2 mL dilution (benzyl alcohol: 9 mg/mL) <sup>a</sup> vs standard saline <i>n</i> = 93 Multiple locations (upper face, crow's feet, <i>n</i> = 60, neck, <i>n</i> = 15, axillary region <i>n</i> = 18)	VAS (0–10)	1.2 (with preservative) vs 4.5 for the upper face 0.6 (with preservative) vs 3.9 for the neck 0.9 (with preservative) vs 5.1 for the axillary region ( <i>P</i> = 0.000)	The preservative containing solution was always applied on the right side
Allen and Goldenberg [30] 2012 USA	RCT Randomized Double blind Split-face design Dysport (Abo-BoNT-A) Diluted with 2.5 mL of preserved bacteriostatic 0.9% sodium chloride injection, USP (Hospira, Inc., Lake Forest, IL) or standard saline <i>n</i> = 20 (glabella and crow's feet)	VAS (0–10)	90% of patients reported less pain on the side injected with preserved saline than on the side injected with preservative-free saline. Pain on the preserved saline side was 60% less than on the preservative-free side	0.1 mL injected per injection point

VAS: visual analogue scale.

<sup>a</sup>Probably (the source of the benzyl alcohol was Abbot Laboratories, North Chicago, IL, USA).

### What is the evidence for reducing injection pain?

BoNT-A is delivered by subcutaneous or intramuscular injection. Pain thresholds amongst patients vary quite considerably, but reduction in injection pain would be welcomed by all.

There are several consensus statements in the literature advocating the use of preservative in the saline which is used for the dilution of the botulinum toxin [27] Here, we examine the evidence for its use.

### Randomized controlled trials and meta-analysis

There is no meta-analysis available to date using saline with preservative to reduce injection site pain. A total of three clinical trials can be found (Table 61.7).

Three small studies focused on the effect of adding a preservative to the saline used for the dilution of BoNT-A. Two were small randomized double-blinded RCTs, one using 100U of Ona-BoNT-A with a 5 mL dilution and one using a 2.5 mL dilution for

Abo-BoNT-A [28,30]. Similar results are reported from a nonrandomized trial by Sarifakioglu and Sarifakioglu [29]. All three trials point to a decreased pain sensation when adding saline with a preservative (benzyl alcohol) to the different toxins.

The reasons for that might be the anesthetic qualities of the added benzyl alcohol [31] or a more physiological pH or osmotic pressure (A. Pickett personal communication). However, one has to be aware that the addition of benzyl alcohol as a preservative may carry a small risk of contact sensitization [32].

### Summary

To summarize, although the evidence is limited to small trials only, the results suggest reduction in injection pain with the addition of saline with benzyl alcohol as preservative. As injection pain reduction should be a goal of all injected treatments, the use of saline with benzyl alcohol as preservative might be worth a try. Saline with benzyl alcohol as preservative is not currently available everywhere (e.g., not in Germany).

### What is the evidence that BoNT-A may be used for the prevention of wrinkles and folds?

With chronologic and exogenous aging, wrinkles and lines become more apparent, and studies conclude glabellar and forehead lines show significant association with advancing age [1]. Prevention of an aged appearance can therefore be associated with slowing the development of wrinkles and folds, so it is appropriate to explore the question of the evidence that BoNT-A might be a helpful tool for wrinkle prevention. Not surprisingly, the evidence that can be found is very limited. There are no cohort studies, although theoretically a nested case-control study in a large cohort study designed for a different purpose might be an option. Randomized clinical trials – even case cohorts – are not feasible for time periods which extend to several years.

However, two studies were found using Ona-BoNT-A: (1) a twin study (just one pair of identical twins) from Binder [33] and a case cohort study from Dailey *et al.* [34]. In the Binder study, identical twin sisters are described. One received Ona-BoNT-A in the forehead and glabellar region (approximately two to three times each year over 13 years). The other twin received the product only twice (in the forehead and glabellar region, 3 and 7 years previously). Visible forehead and glabellar lines were not evident in the regularly treated twin but were evident in the minimally treated twin. Untreated facial areas (e.g., nasolabial folds) showed comparable aging in both twins.

In the Dailey study (2011), patients ( $n = 45$ ) received repeated injections of 20 U Ona-BoNT-A at 4-month intervals in the glabellar area. Wrinkle severity gradually improved over a total study period of up to 26 months and was still better than baseline at the last time point (6 months after the last injection). A similar study on Inco-BoNT-A exists. In this analysis, phase 3 trial data on the glabella were reanalyzed for repeated injections up to 24 months and eight injection visits with mostly 20 U (although some arms started with 10 or 30 U). Efficacy gradually improved from the first to the last visit [35]. A comparable study is the study of Moy *et al.* [37] focusing on Abo-BoNT-A in the treatment of the glabella. However, in this study the total observation period was limited to 13 months and five consecutive treatments only.

### Summary

The evidence that BoNT-A prevents the signs of aging is very limited. Besides the twin study that at least covers a 13-year period,

there are only two 2-year studies. Both studies support a possible preventive effect of repeated BoNT-A treatments. Case-control studies should be encouraged with the aim to evaluate minimum doses required and injection intervals necessary.

### Further questions

All the interesting and relevant questions relating to the esthetic use of BoNT-A could not be covered in this chapter. However, an overview of questions which focus on specific anatomical areas, modes of injection, and the intervention as preventative treatment has been provided in this chapter.

### Key points

The treatment with BoNT-A is well established; however, there are still significant gaps in our knowledge base. Even for the four questions we examined, available evidence was extremely variable and often fraught with confounding factors.

### Indication-based questions

Concerning the optimal dosage for the glabella, there is a large amount of evidence arising from clinical trials as well as case cohorts. Based on these trials, the optimal dosage is estimated to be 50 U Abo-BoNT-A (Dysport/Azzalure) and 20 U Ona-BoNT-A (Botox/Vistabel). Nevertheless, one has to be aware that all except one study were performed in overwhelmingly female populations. Therefore, this dosage may be considered a starting dose in men and may be adjusted to muscle mass and muscle activity. In contrast, for the forehead, the available data are very limited. So far there is enough evidence for efficacy, but not for the optimal dosage or injection points. Furthermore, the endpoints of maximum reduction in glabellar lines must be placed into the entire facial esthetic context.

### Procedure-based question

There is some evidence that the addition of preservative may decrease injection pain. Based on this evidence, the usage of saline with preservative (benzyl alcohol) may be suggested. However, larger clinical trials are necessary to turn this into a sound recommendation. It should also be evaluated whether the use of preservative-containing diluents affects the product in any way.

### Prevention through long-term BoNT-A treatment

Finally, the use of BoNT-A as a preventive agent must be considered. Here, the evidence is very scarce. We have a case report and two case series of different durations pointing to a positive, preventive effect of a regular treatment with BoNT-A. It is clear more evidence is needed; for example, a case-controlled study focusing on long-term treated and nontreated patients with controls for other preventive factors would be very helpful.

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**Conflict of interest:** B. Rzany is a consultant and speaker for Galderma, Ipsen and Merz. In 2011 he was also a speaker for Allergan (all manufacturers of BoNT-A).



## SECTION 6 Other important skin disorders

Michael Bigby, editor

### CHAPTER 62

# Cutaneous lupus erythematosus

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## Background

### Definition

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease characterized by the presence of a wide variety of autoantibodies. Skin involvement is common, being present in 55–90% of cases [1]. The characteristic skin lesions can be divided into acute, subacute, and chronic subsets [2]. The acute forms include the malar (butterfly) rash, papular lesions, urticaria, vasculitic lesions, hair loss, and painless mouth ulcers. Subacute cutaneous lupus erythematosus (SCLE) is an uncommon form of cutaneous lupus, described as a clinical subset by Sontheimer *et al.* in 1979 [3]. Chronic discoid lupus erythematosus (DLE; Figure 62.1) tends to be the most persistent of the skin lesions and may lead to unsightly scarring. It is most frequently seen as an isolated entity, but may also occur in SLE. Lupus panniculitis (lupus profundus), neonatal lupus, lupus tumidus, and bullous lupus are less commonly encountered forms of the disease.

### Incidence/prevalence

Accurate incidence or prevalence figures are difficult to obtain because different methods have been used in the reported studies. Many series are hospital based and probably do not reflect the true incidence. Published figures suggest an increasing incidence, but apparent changes in incidence may be because of greater awareness of the condition.

### Etiology

Lupus seems to result from an interaction between genetic, hormonal, and environmental factors [4]. SLE is known to be associated with the production of a large range of autoantibodies. In certain specific subsets, such as neonatal lupus, their role in pathogenesis is now clearly established. The greatest risk factor is female sex (the female:male ratio is 9:1), and the highest prevalence is in the child-bearing age group. The genetic hypothesis is supported by familial

clustering of lupus and the association between certain human leukocyte antigen types with particular subsets of lupus [5,6].

Evidence for a viral etiology has not been conclusive [7]. A detailed discussion is beyond the scope of this text.

### Prognosis

Mortality is associated with severe systemic disease, and is highest with renal and central nervous system involvement. Skin involvement, while not associated with mortality per se, frequently produces scarring, with considerable morbidity, both physical and psychological.

### Diagnostic tests

Diagnosis of cutaneous lupus can generally be made by clinical examination. A skin biopsy is required in cases of doubt. Autoantibody tests may be positive in cutaneous lupus but do not necessarily imply systemic disease. Specific antibodies, notably antiRo antibody, are strongly associated SCLE and neonatal lupus.

### Aims of treatment

Doctors aim to stop inflammation and prevent further damage. Unfortunately, there may be marked residual pigmentary changes (most marked in dark-skinned individuals) and skin atrophy. People with facial DLE may be disappointed by this outcome, as quality of life remains impaired. Early diagnosis and treatment are important to prevent extensive scarring.

### Relevant outcomes

- Improvement in participant global score;
- improvement in redness, thickness or scaling of lesions;
- reduction in extent of lesions;
- total clearing;
- no change or worsening of skin lesions;
- development of new lesions.



**Figure 62.1** Lesions of DLE, showing scarring and changes in pigmentation.

A scoring system, the cutaneous lupus activity and severity index (CLASI), has been proposed to quantify activity and damage in cutaneous lupus [8]. CLASI is a promising move towards improved consistency in clinical trials.

### Methods of search

We searched the Cochrane Library (2012), Medline (1950s to June 2012), Embase (1988 to June 2012) Science Direct (2001–June 2012) and the Cochrane Central Register of Controlled Trials. We included all randomized controlled trials (RCTs) and controlled trials. Where no controlled trials were found, we report briefly on observational studies.

## Questions

### What are the effects of antimalarial treatment in cutaneous lupus?

#### Chloroquine or hydroxychloroquine

##### Benefits

We found one systematic review [9] and two RCTs.

Ruzicka *et al.* studied 39 people with DLE and 19 with SCLE, comparing hydroxychloroquine, 400–1200 mg/day, with acitretin, 50 mg/day, over 8 weeks [10]. Treatment arms were similar in terms of age, sex, and extent of disease, but SCLE was more strongly represented in the hydroxychloroquine group. Complete clearing or marked improvement occurred approximately equally in the two groups (50% vs 46%). Four participants dropped out because of treatment side effects (all in the acitretin arm) and three because of total clearing of lesions (all in the hydroxychloroquine arm). In the study by Bezerra *et al.*, 33 people were randomized to receive either 100 mg/day clofazimine (16 participants), or 250 mg chloroquine daily (17 participants). Skin lesions ranged from chronic discoid to acute lupus. There was no significant difference in the response rates at 6 months: 82% in the chloroquine group and 75% in clofazimine group [11].

We found three RCTs of antimalarials in non-life-threatening SLE. In a Canadian study, people taking hydroxychloroquine for

SLE were randomized to continue the drug ( $n = 25$ ) or to take placebo ( $n = 22$ ) [12]. At 6 months, 16 of the 22 on placebo and 9 of 25 in the active arm had experienced disease flares, a 2.5-fold increase in the untreated participants. Skin lesions were not specifically described. Williams *et al.* compared hydroxychloroquine, 400 mg/day, with placebo in 71 people with mild SLE over 48 weeks [13]. Although the study was designed to determine the effect of the trial drug on joint disease, the cutaneous, neurological, and cardiopulmonary systems were also evaluated. Placebo and active groups both improved, but overall there was no significant difference in the outcome of skin lesions between the two groups at any stage in the study. The third RCT involved 23 participants, 11 randomized to receive chloroquine and 12 to receive placebo [14]. The chloroquine-treated group showed less “skin activity” than the placebo group (9% compared with 42%; 95% confidence interval, 9–74%), but skin lesions and outcome measures were not clearly described. Overall, patients taking chloroquine experienced fewer flares and required lower doses of steroids.

We found one double-blind but nonrandomized trial comparing hydroxychloroquine with placebo in DLE [15]. Forty-nine people were treated for 1 year: 24 with hydroxychloroquine and 25 with placebo. Results at both 3 and 12 months indicated that hydroxychloroquine was superior to placebo.

We found many observational reports of chloroquine or hydroxychloroquine in cutaneous lupus [16–22]. Christiansen reviewed 13 case series up to 1956 and added his own, giving data on a total of 414 people treated in these studies [16]. He noted that 265 (64%) experienced complete clearing or marked improvement. His series was notable for the duration of treatment (18–53 weeks) and the careful description of outcome, but was flawed by the absence of a parallel control group and the high dose of chloroquine (500–750 mg daily). An open trial of chloroquine in patients with lupus tumidus suggests that it may be useful in this condition [23].

##### Harms

Adverse events were described in 17 of 30 people taking hydroxychloroquine [10]. Symptoms included dry skin ( $n = 8$ ), itching ( $n = 5$ ), and gastrointestinal disturbance ( $n = 5$ ). The most frequent side effects described by Kraak *et al.* were gastrointestinal (eight in hydroxychloroquine arm vs three in placebo arm) and cutaneous (four in hydroxychloroquine arm vs three in placebo arm) [15]. One person developed a severe retinopathy while taking hydroxychloroquine, after having taken chloroquine for several years at a higher than recommended dose (1200 mg/day). Retinal toxicity is discussed by Houpt [24]. There is little evidence to support regular blood monitoring [25]. A meta-analysis of toxicities emphasizes the low level of toxicity of antimalarials [26]. A small RCT in 20 pregnant women with lupus erythematosus, 10 taking hydroxychloroquine, showed no adverse effects in either mothers or babies [27].

##### Comments

While chloroquine and hydroxychloroquine are currently “standard of care” in cutaneous lupus, trials are flawed by a lack of placebo group and inclusion of different types of cutaneous lupus erythematosus (CLE). SLE trials do not provide clear descriptions of mucocutaneous lesions, making interpretation difficult.

We have not found evidence of a difference between hydroxychloroquine and chloroquine in the treatment of CLE or any information regarding dosage in CLE, in relation to either efficacy or toxicity.

## Amodiaquine and quinacrine

### Benefits

We found no RCTs or controlled trials. Wallace has reviewed the literature on quinacrine, finding 20 observational trials [28]. Cutaneous subsets and outcome measures were not clearly defined. Smaller observational studies of amodiaquine have been published [29,30].

### Harms

Central nervous system, gastrointestinal, and cutaneous adverse effects have been reported.

## Combinations of antimalarials

### Benefits

We found no controlled trials. There are five case series and a case report of the combination of chloroquine and quinacrine [31–35].

### Harms

Yellow skin discoloration, photophobia, insomnia, and nausea were noted by some people but did not usually require withdrawal of treatment.

## Intralesional antimalarials

### Benefits

We found two observational studies of intralesional chloroquine [36,37].

## What are the effects of systemic steroids in cutaneous lupus?

### Oral steroids

#### Benefits

We found no RCT. We found one observational study and a case series in combination with an antimalarial [38,39].

#### Harms

“Mild cushingoid features” were noted in two people taking oral steroids during the above study [38]. A recent review of side effects of low-dose glucocorticoids suggests that the harms associated with these agents may not be as serious as traditionally believed [40].

#### Comments

There is not sufficient evidence to judge the efficacy of oral steroids in cutaneous lupus.

## What are the effects of other oral agents in cutaneous lupus?

### Clofazimine

#### Benefits

We found one small RCT comparing clofazimine with chloroquine [11]. There was no significant difference in the response rates at 6 months: 82% (14/17) in the chloroquine group and 75% (12/16) in the clofazimine group. We found four observational studies [41–44].

#### Harms

A pink or red discoloration and darkening of the skin resulting from the deposition of clofazimine has been recorded. Dry skin, keratosis pilaris, and a transient rise in transaminases have been reported. Arbiser and Moschella have reviewed the toxicity of clofazimine [45].

### Comments

A small RCT suggests that clofazimine may be useful in treatment of cutaneous lupus but the quality of evidence is poor, due to small numbers and lack of a placebo group.

## Dapsone

### Benefits

We found no RCTs or controlled trials of dapsone. Case series and case reports describe the use of dapsone in people with various forms of cutaneous lupus, in particular bullous lupus and urticarial vasculitis [46–56]. Data are summarized by Duna and Cash [57].

### Harms

Side effects described include nausea, vomiting, headache, fatigue, hemolysis, methemoglobinemia, and leucopenia. Mok *et al.* have reviewed the toxicity of dapsone [58].

### Comments

There is no adequate evidence to guide clinical practice.

## Methotrexate

### Benefits

We found no RCTs, but did find one controlled trial of methotrexate in systemic lupus [59]. A double-blind study reported that 12 of 20 people in the active arm and 16 of 21 in the placebo arm had cutaneous lesions, declining to three in the active arm but remaining unchanged in the placebo group. The skin lesions and outcome measures are not described. A retrospective study of cutaneous lupus recorded an improvement in 42 of 43 people [60]. A second retrospective study of 139 patients had similar findings [61]. We found small observational studies and case reports describing improvement in a variety of skin lesions of lupus [62–71].

### Harms

Problems encountered included dyspepsia, mouth ulcers, thrombocytopenia, and a rise in transaminases, but no increased rate of infection. Discussions of methotrexate toxicity have been published [72,73].

### Comments

The evidence for an improvement in skin lesions is too limited to allow any definite conclusions, although it may be a useful drug.

## Retinoids

### Benefits

We found one RCT, in which there was no placebo group and the two treatment groups were not matched for type of CLE [10]. We found three uncontrolled trials, and several case reports of oral or topical retinoids in chronic cutaneous lupus [74–84].

### Harms

Retinoids are teratogenic. Side-effects were recorded more commonly with acitretin (27 of 28 people) than with chloroquine [10]. Dry lips, dry skin, itching, and hair loss were most common. Raised serum triglycerides were noted in five of 18 people. All improved with dose reduction and resolved when therapy was discontinued. Retinoid toxicity has been reviewed by Lowe and David [85].

### Comments

There is insufficient evidence to assess the value of retinoids in cutaneous lupus. The available evidence suggests that efficacy is

similar to that of hydroxychloroquine, but that side effects appear to be more frequent.

## Thalidomide

### Benefits

We found no RCTs or controlled trials. There have been numerous uncontrolled studies, and several case series are reported [86–97]. In an uncontrolled Brazilian study on refractory cutaneous lupus, 60 of 65 participants experienced complete remission. Lesions ranged from chronic DLE to acute rashes. There was an 82% relapse rate on stopping the drug [86]. Similar results have been reported in smaller series [87,96].

### Harms

Thalidomide is teratogenic. Varying incidences of paresthesia and electroneurographic changes have been reported. Other side effects include drowsiness, dizziness, vertigo, dreams, mood changes, weight gain, and constipation. Calabrese and Fleischer have reviewed the side effects of thalidomide [98]. There is a single case report on the use of lenalidomide in the treatment of DLE [99].

### Comments

The evidence for efficacy is inadequate, relying on observational studies and case reports.

### Implications for clinical practice

There is no evidence from controlled trials to support the use of thalidomide in CLE.

Current recommendations for people taking thalidomide include patient education about risks of pregnancy and significance of paresthesia, a three-monthly clinical examination, and electrophysiological studies, if indicated.

## Mycophenolate mofetil

### Benefits

A number of studies, including an open trial, case series, and case reports, have been reported, with conflicting results [100–104]. An RCT for induction treatment of renal lupus found that cutaneous lupus improved, but no details are given [105].

### Harms

Mycophenylate mofetil (MMF) appears to be generally well tolerated.

### Comments

Current data make it impossible to comment on the possible role of MMF in treatment of CLE.

## What are the effects of biological agents in cutaneous lupus?

### Rituximab

#### Benefits

An RCT has failed to demonstrate a difference between rituximab and placebo in people with moderate to severe systemic lupus. A number of patients with muco-cutaneous lesions were included, but details are insufficient to allow any conclusions [106].

Analysis of French rituximab registry data demonstrated a 70% improvement in cutaneous lesions among people with SLE [107]. The study was seriously flawed, as it was not a trial, rituximab was not compared with another agent, participants were not equally distributed, and skin lesions were not described. There are case

reports and case series describing the use of rituximab in SLE. These have been summarized [108].

#### Harms

Severe adverse reactions have been reported, including infusion reactions and severe infection [107].

#### Comments

Currently, there is no convincing evidence to support the use of rituximab in the treatment of CLE.

## Belimumab

### Benefits

We found two RCTs of placebo versus belimumab 10mg/kg [109,110]. Belimumab was a little more effective than placebo in reducing flares of SLE (SLE response index at 52 weeks was 43.2% vs 33.5%). No analysis of skin involvement was reported. A study using the same design in different populations showed similar results.

### Harms

Infusion reactions and severe infection were reported in both placebo and active groups in both studies.

### Comments

There is insufficient evidence to support the use of belimumab in CLE.

## Efalizumab

### Benefits

A small open trial and a case report in cases of DLE have been reported [111,112].

### Comments

No comments are possible owing to paucity of data.

## Other biological agents

Tumor necrosis factor alpha antagonists: the complex interaction between these agents, SLE, and skin lesions is discussed elsewhere [113].

The use of other biological agents has been directed at controlling systemic flares, and there is currently no evidence to guide clinicians in their use in CLE [114].

## Other systemic agents

Short series or case reports exist for a wide range of agents, including azathioprine [115–119], cyclosporine [120–123], phenytoin [124], sulfasalazine [125,126], immunoglobulins [127–129], and interferon alpha [130,131], but there is no robust evidence for their effectiveness and we will not discuss these agents further.

## What are the effects of topical agents in cutaneous lupus?

### Topical steroids

#### Benefits

We found two RCTs of potent topical steroids [132,133]. The first study compared 0.025% fluocinolone acetonide and 0.1% betamethasone valerate used for 3 weeks [132]. Symmetrical skin lesions were used, and the participants were randomized to use the creams on the right or left side of the body. Betamethasone valerate appeared to be superior in 15 of 25 (60%) participants.



In a 12-week crossover study, 0.05% fluocinonide (a potent steroid cream) was compared with 1% hydrocortisone (a low-potency steroid cream) [133]. After 6 weeks, an excellent response was seen in 10 of 37 people (27%) using fluocinonide and in 4 of 41 people (10%) using hydrocortisone cream. This result suggests that high-potency steroid cream is more effective than low-potency steroid cream.

We found one controlled trial, comparing fluocinolone acetone with ointment base; 17 of 20 people (85%) showed greater improvement with the steroid than with base alone [134].

We found six observational studies of topical steroids [135–140]. A total of 263 people were treated in these trials, 220 (84%) of whom experienced complete clearing or marked improvement in the treated areas.

### Harms

Skin irritation was noted by three people using hydrocortisone, and a burning sensation by one person using fluocinolone [133]. No side effects were reported in the other controlled trials. In the uncontrolled trial of methylprednisolone aceponate in 322 people with various dermatoses, local side effects such as burning, itching, pain, and inflammation were observed in 22 people (7%) [136]. Toxicity of topical steroids has been reviewed by Hengge *et al.* [141].

### Comments

All the controlled trials of topical steroid were of short duration, but the evidence supports the use of potent topical steroids in DLE.

Although topical steroid use may be associated with skin atrophy, it is probably relatively unimportant in DLE, which produces severe scarring and atrophy in itself.

## Intralesional steroids

### Benefits

We found four case series, involving 114 people. There was marked improvement or clearing in 91 participants (80%) [142–145].

### Harms

Skin thinning (atrophy) was noted in a small percentage of people in the above studies.

## Calcineurin antagonists

### Benefits

We found four RCTs and one nonrandomized study.

An RCT involving 20 patients comparing 0.1% tacrolimus with 0.05% clobetasol found no difference [146]. Small numbers, lack of intention to treat, mixed subsets of CLE, and short duration limit the value of this study.

A placebo-controlled randomized trial found 0.1% tacrolimus to be superior to the vehicle initially [147]. The beneficial effect was not sustained at 84 days.

An RCT comparing 1% pimecrolimus with 0.5% betamethasone valerate found the two agents comparable at 8 weeks [148]. Small numbers reduce the value of their findings.

An RCT comparing 1% pimecrolimus with placebo in 25 patients with DLE and SCLC found no difference [149].

There are numerous cases series and case reports. Sticherling includes a comprehensive summary of all published work on this topic [150].

### Harms

RCTs using these agents for other conditions have identified irritation and a sensation of burning as common in the early stages of treatment. Carcinogenesis has been raised as a potential concern.

### Comment

Topical tacrolimus appears to be as effective as ultrapotent topical steroids and the side-effect profile may be better.

## What are the effects of nondrug treatments in cutaneous lupus?

### Sunscreens

#### Benefits

We found one double-blind intra-individual trial on the efficacy of three commercially available sunscreens in the prevention of the skin lesions in SLE. Protective efficacy on exposure to ultraviolet light varied from 30 to 100% [151]. In a placebo-controlled RCT examining response to ultraviolet light, broad-spectrum sunscreen significantly reduced ultraviolet-induced skin lesions in people with CLE [152].

A clinical RCT was conducted and completed at the end of 2013 (registration no. NCT01146444).

We found one further open-label study [153].

#### Comments

There is evidence to suggest that sunscreens are beneficial in the prevention of CLE.

## Surgery

### Benefits

We found no RCTs or controlled trials. We found six reports describing 17 patients treated with either dermabrasion or excision and grafting [154–159].

#### Comments

There is insufficient evidence to comment about surgery.

## Ultraviolet light

### Benefits

We found one controlled trial of UVA1 (350–440 nm) in 11 people with systemic lupus [160]. Disease activity was measured by the SLE disease activity index (SLEDAI score), a 24-item score that measures SLE activity [161], but skin lesions were not specifically described. A nonsignificant improvement in Raynaud's phenomenon and rash (type not specified) was noted.

We found two observational studies [162,163]. Sonnischen *et al.* successfully treated a person with DLE [164]. We also found case reports describing the use of extracorporeal photopheresis in cutaneous lupus [165–167].

### Harms

No adverse events were reported in the above studies.

#### Comments

Although the trial reported by Polderman *et al.* [160] was double blind, the findings cannot be interpreted with confidence because the numbers were small and the two arms (nine active treatment, two placebo) were disproportionate.

There is currently insufficient evidence to comment on the use of this modality. There is no evidence to indicate the relative risk of inducing a flare in this light-sensitive disorder.

## Laser treatment

### Benefits

We found no RCTs or controlled trials. We found two case series and five case reports [168–174] using various forms of laser.

## Harms

Transient pigmentation was seen in some people.

## Comment

Data are too fragmented to allow any conclusions.

### Key points

- We found limited evidence that potent topical steroids, tacrolimus cream, chloroquine, and acitretin are beneficial in cutaneous lupus.
- We found very few RCTs of treatment of cutaneous lupus and only a few controlled trials.
- We found many uncontrolled studies, some involving large numbers of people, followed for several years, particularly relating to older treatments.

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# Dermatomyositis

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## Background

### Definition

Dermatomyositis (Figure 63.1) is one of the idiopathic inflammatory myopathies [1,2]. In a set of criteria to aid in the diagnosis and classification of dermatomyositis and polymyositis, first proposed by Bohan and Peter in 1975 [3,4], four of the five criteria are related to the muscle disease:

- 1 progressive proximal symmetrical weakness;
- 2 elevated muscle enzymes;
- 3 abnormal electromyogram (EMG);
- 4 abnormal muscle biopsy;
- 5 presence of compatible cutaneous disease.

Unfortunately, these criteria are not sensitive in identifying the full spectrum of patients with idiopathic inflammatory dermatomyopathy. It has subsequently been recognized that there are many patients with compatible cutaneous disease who never develop any manifestation of muscle disease, such as weakness or abnormal changes on muscle biopsy, EMG, or magnetic resonance imaging (MRI) studies. Sontheimer [5] has used the term “amyopathic dermatomyositis” (ADM) for those who fulfill these criteria for at least 6 months in the absence of disease-modifying therapies such as corticosteroids and/or immunosuppressive agents. Juvenile dermatomyositis is traditionally defined as disease onset before 16 years of age.

### Incidence/prevalence

Dermatomyositis is a rare disorder. It may be slightly more frequent in women, and all ethnic groups are affected. It has been estimated that dermatomyositis or its related condition polymyositis occur in 5.5 patients per million. However, this figure includes patients with polymyositis and dermatomyositis and most likely does not include patients with ADM. More recently, the incidence of clinically ADM was noted to be 2.08 (95% confidence interval [CI], 0.39–3.77) per 1 million persons in a population-based study, making these cases comprise approximately 20% of all dermatomyositis cases [6].

## Etiology

The etiology of dermatomyositis is unknown. The mechanism behind the skin disease likely differs from that of the muscle disease. Dermatomyositis appears to result from a complement-mediated inflammation and destruction of capillaries with subsequent ischemic muscle damage, whereas polymyositis is thought to be caused by cytotoxic CD8+ T cells damaging muscle fibers.

### Prognosis

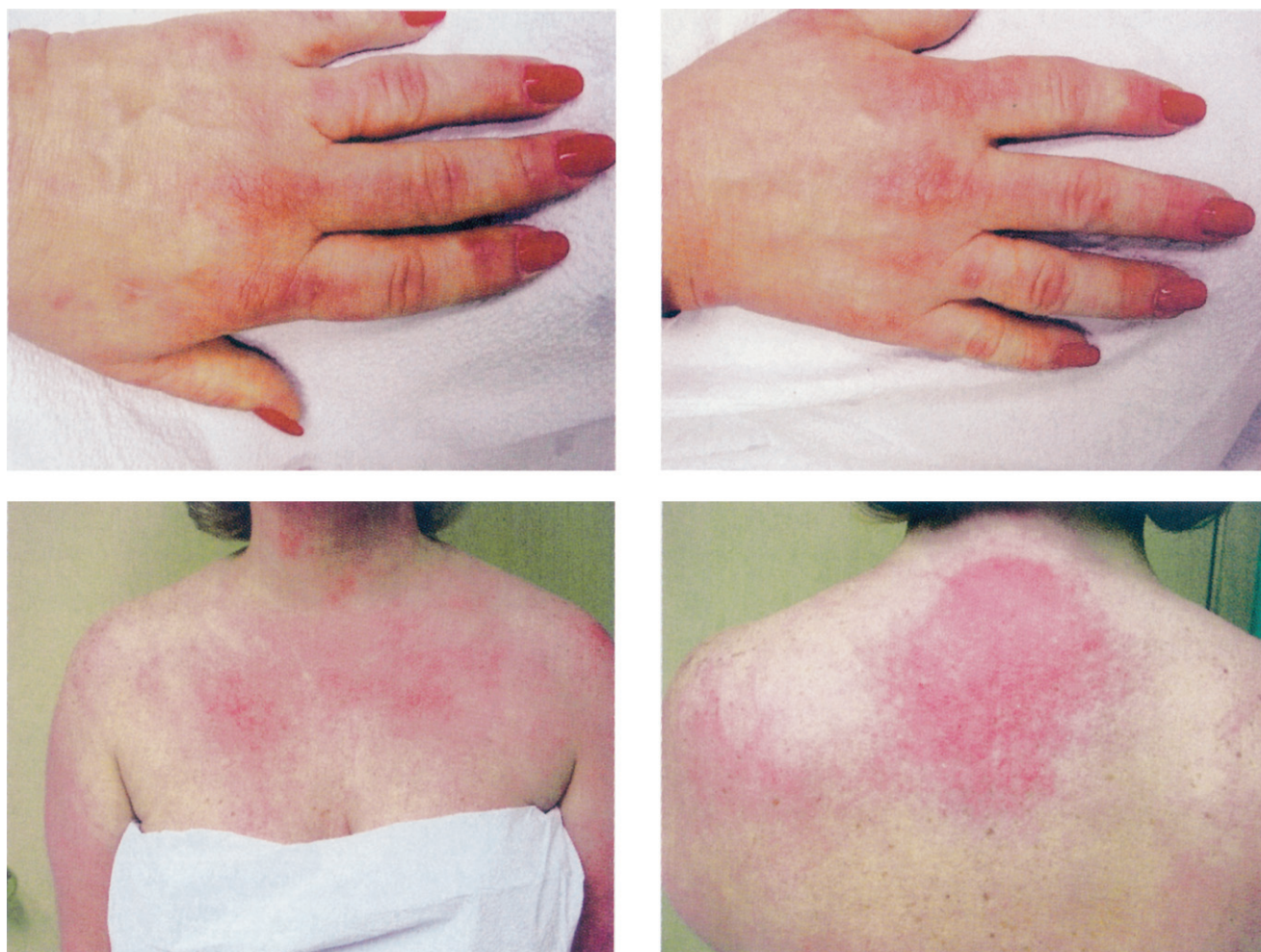
In the patient with ADM, the prognosis is good in the absence of malignancy or pulmonary disease. For patients with muscle disease, the prognosis depends on the severity of the muscle disease, the presence of lung disease, esophageal dysfunction, cardiac disease, and/or malignancy. Children and adolescents with dermatomyositis often develop calcinosis, which can result in disability or discomfort, but are not considered to have an increased risk of malignancy.

### Diagnostic tests

The diagnosis of ADM is confirmed by clinical–pathological correlation. The pattern of the skin disease is relatively characteristic, and when an interface dermatitis is demonstrated on skin biopsy, the diagnosis may be relatively firm. However, some subtle cases can be confused with cutaneous lupus, and immunofluorescence studies of skin biopsies can be helpful in making this distinction [7,8]. For patients with myositis, the diagnosis of dermatomyositis is confirmed by the presence of typical muscle symptoms and findings, together with elevated muscle enzymes, or an abnormal EMG, MRI, and/or an abnormal muscle biopsy.

### Aims of treatment

Treatment provides control of the muscle inflammation and allows the patient to return to normal function; the patient might otherwise become disabled from the weakness. The skin disease is often symptomatic, often associated with prominent pruritus, and is cosmetically displeasing. The goal of therapy is therefore to relieve the



**Figure 63.1** This patient presented for the evaluation and treatment of her skin condition, which had been present for the past 6 months. A previous biopsy had revealed an interface dermatitis and her antinuclear antibody was positive. A working diagnosis of lupus erythematosus was made. Treatment with sunscreens and topical corticosteroids were ineffective. Hydroxychloroquine administration resulted in a severe cutaneous drug reaction that required hospitalization. Clinical examination on referral revealed cutaneous findings of dermatomyositis.

symptoms and improve the patient's quality of life. Some patients with dermatomyositis have an associated malignancy, and treatment of the malignancy may in some patients result in a control of the disease process. In children with dermatomyositis, treatment also aims to prevent calcinosis, or to eradicate calcinosis if it does occur.

### Relevant outcomes

Return of the patient to normal muscle function and improvement in the quality of life for those with skin disease are important measures of outcome. Improvement in lung function is important in patients with pulmonary disease. In addition, identification and treatment of a potential malignancy is important. Outcome measures of muscular and extramuscular function have been defined [9,10]. In addition, outcome instruments to evaluate the response of cutaneous dermatomyositis to therapy have recently been developed. The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and the Dermatomyositis Skin Severity Index (DSSI) have recently been validated and will be valuable for future studies [11–13].

### Methods of search

The databases of the Cochrane Skin Group, the *Cochrane Library* to issue 1, 2012, and Medline and Embase between 1968 and July 2012 were searched for articles reporting trials of therapy of skin disease, or dermatomyositis, or the relationship of dermatomyositis to malignancy. Both Embase and Medline were searched using the Ovid search engine at Nottingham University. The searches involved the following terms:

- The relationship of dermatomyositis to cancer (malignancy, neoplasia).
- Treatment of skin disease in patients with dermatomyositis (idiopathic inflammatory myopathy, polymyositis, juvenile dermatomyositis).
- Treatment of dermatomyositis with any of the following agents: antimalarials (hydroxychloroquine, chloroquine), corticosteroids (prednisone, methylprednisolone), dapsone, thalidomide, methotrexate, mycophenolate mofetil, azathioprine, intravenous immunoglobulin (IVIG), rituximab, etanercept, infliximab, adalimumab, eculizumab, abatacept, anakinra, physiotherapy, physical therapy, plasma exchange, plasmapheresis, cyclophosphamide,

cyclosporine, tacrolimus, FK506, probenecid, colchicine, minocycline, alendronate, pamidronate, diltiazem, warfarin, and sunscreens.

## Questions

### What is the risk of malignancy in the patient with dermatomyositis or amyopathic dermatomyositis?

Population-based studies from Scandinavia clearly demonstrate an increase in the risk of cancer in dermatomyositis, while the modest increase in polymyositis is explained primarily by diagnostic suspicion bias and is not reflected in an increase in mortality (Table 63.1) [14–21]. More recent American and South Australian studies also support this finding [22,23]. It is also clear that these patients have an increased risk for ovarian cancer [14,16,18,19,24–26]. What has not been clear is whether these data are applicable to other populations such as Southeast Asians, African-Americans, or other ethnic groups. More recently, data from Southeast Asian populations support a higher risk of malignancy in patients with dermatomyositis than with polymyositis as well [27–29].

A study from Australia [15] called into question much of the data that have been based on clinical diagnosis. It does appear that dermatomyositis and polymyositis are not the same disease and that their histopathological abnormalities differ significantly and are recognizable by muscle pathologists. Therefore, there may exist a group of patients who were thought to have polymyositis but who might be classified as having dermatomyositis sine dermatitis. This concept is intriguing and might explain why some studies have shown little difference in the prevalence/incidence of malignancy in the two groups. In addition, the existence of this subset might well explain some of the differences that are observed in the studies of therapy (see later).

Regarding patients with ADM, a systematic review of the available published cases previously suggested that these patients are also at increased risk for cancer, as well as interstitial lung disease [17]. Since that time, additional literature has supported that patients with amyopathic disease still have a risk for associated malignancy [30]. In one retrospective review based in the USA, the prevalence of interstitial lung disease was found not to be different between patients with classic and ADM [31]. Other data suggest that patients with skin-limited disease may even have an increased risk of pulmonary disease in some populations. One of the difficulties regarding investigations of associations with ADM relates to the manner in which ADM is diagnosed. Because the Sontheimer criteria do not require any testing beyond muscle enzymes, many of the patients defined as having ADM might not actually have amyopathic disease if they were analyzed using all of the available modalities (MRI, muscle biopsy, etc.).

Another issue that is discussed almost universally in the case-control studies is whether the use of immunosuppressive drugs is associated with an elevated risk of subsequent malignancy. In the Scandinavian studies [14,16,18,19], it appears that there is no increase in the prevalence of malignancy in patients who have been treated with an immunosuppressive agent; however, there are many individual case reports of subsequent malignancy in dermatomyositis patients. Several reports [32,33] have linked the use of methotrexate with lymphoma associated with Epstein-Barr virus. Some, but not all, of these patients can have a spontaneous resolution of their lymphoma when the drug therapy is stopped.

### Are there clinical or laboratory findings in dermatomyositis patients that suggest underlying malignancy?

Several studies have suggested that there might be certain clinical or laboratory features that are associated with a greater risk of malignancy (Table 63.2) [14,18,20,34–59]. Most studies, including population-based studies from Scandinavia and Scotland, have shown that advanced age is a significant risk factor for malignancy [14,18,20]. Clinical findings of severe vasculopathy (or vasculitis), such as cutaneous necrosis, ulceration, nodules, and/or periungual infarcts, have also been associated with malignancy [42,44,45, 51,54,60]. Although many studies claim that these findings represent vasculitis, most of them do not present skin biopsy data. Hunger *et al.* provide the only biopsy-based data that cutaneous vasculitis may be a sign of internal malignancy [43]. However, the numbers are too small for firm conclusions to be drawn, and other studies have rejected such an association [49,50,52]. Elevated erythrocyte sedimentation rates have been correlated with malignancy. In contrast, patients with arthralgia/arthritis, Raynaud's, interstitial lung disease, and certain autoantibodies, findings that can be found in association with each other in the "antisynthetase syndrome," have lower prevalences of malignancy in many studies [56]. In general, there have been no consistent associations with regard to muscle disease severity (i.e., strength or enzymes), cutaneous findings (other than the necrosis), or constitutional symptoms that appear to distinguish idiopathic from paraneoplastic dermatomyositis.

Novel sets of autoantibodies have been found to be associated with certain clinical subsets of dermatomyositis. In particular, cancer-associated dermatomyositis, has been noted to be associated with the anti-p155 autoantibody [57–59]. Anti-CADM-140 autoantibodies are associated with clinical ADM, and in some populations rapidly progressive interstitial lung disease, whereas anti-Mi-2 autoantibodies are associated with classic dermatomyositis without either malignancy or pulmonary disease [59]. One series has suggested that patients with anti-CADM-140 autoantibodies have a characteristic cutaneous presentation suggestive of severe vasculopathy [61]. In addition, it has recently been demonstrated that most patients with malignancy-associated dermatomyositis have antibodies to either transcription intermediary factor 1 $\gamma$  (TIF-1 $\gamma$ ) or nuclear matrix protein NXP-2 [62]. These autoantibodies may be useful for diagnosing certain subsets of clinical disease in dermatomyositis in the future, and therefore aid in guiding disease management.

### How should the patient with dermatomyositis/amyopathic dermatomyositis be assessed for possible cancer?

The search for malignancy in patients with dermatomyositis should include a careful history, full physical examination, and standard laboratory evaluation (complete blood count, comprehensive metabolic panel, and stool Hematest). Any abnormalities found should be thoroughly investigated. It remains controversial whether age-appropriate malignancy screening versus more aggressive malignancy screening is supported by the best available evidence. At the very least, a malignancy work-up should include a chest radiograph as well as tests that would be ordered in a "healthy" person of the same age, sex, and ethnic group as the patient with newly diagnosed dermatomyositis (for example, it is recommended that persons over 50 years of age should have a colonoscopy). Many authors have suggested that "blind" screening tests (beyond those mentioned

**Table 63.1** What is the risk of malignancy in patients with dermatomyositis or ADM?

First author, ref.	Population-based?	Patients with CA in the DM/ADM group	Patients with CA in the PM group	Statistically different?	Comment(s)
Sigurgeirsson [19]	Yes	59/392	37/396	Both groups had elevated rate vs controls. Cancer mortality raised only in DM	Ovarian cancer increased 17-fold Authors suggest increase in PM due to more extensive evaluation (diagnostic suspicion bias)
Airio [14]	Yes	19/71	12/175	SIR DM: 6.5 PM: 1.0	Risk rises with age, slight risk for overlap patients Nonmelanoma skin cancers, myelofibrosis, polycythemia vera, in-situ cervical cancer, and 12 preceding cancers eliminated Overrepresentation of ovarian cancer
Chow [16]	Yes	31/203	26/336	SIR DM: 3.8 PM: 1.7 reduced to 1.0 by 3rd year following diagnosis	Excess lymphoma/leukemia Surveillance for prolonged periods may not be needed
Hill [18]	Yes	115/618	95/914	SIR DM: 3.0 PM: 1.3	Plan for evaluation based on the results of their study suggested data derived from Swedish, Finnish, and Danish studies, but included additional follow-up from Denmark and Finland
Buchbinder [15]	Yes, population-based, retrospective cohort study based on pathological findings	36/85	57/321	OR All cases: 2.6 DM: 6.2 PM: 2.0 IBM: 2.4 JDM: 29.0 Myositis with CTD: 4.6	Authors believe diagnosis of DM possible without the presence of a rash, based on the changes observed in the muscle biopsy Increased malignancy rate found in all groups, including children
Stockton [20]	Yes	50/286 Women: 30/189 Men: 20/97	40/419 Women: 28/244 Men 12/175	SIR DM: 7.7 PM: 2.1	27 patients with DM and 31 with PM had cancer before DM/PM diagnosed; not known whether any of these patients had metastatic disease at the time of diagnosis. Increase in ovarian, cervical, and lung cancer in DM and in Hodgkin's disease in PM found
Zantos [21]	Meta-analysis of 4 CC cohort studies	97/513	56/565	OR DM: 4.4 PM: 2.1	Increased malignancy in the preceding and subsequent 4 years
Antiochos [22]	Retrospective review, 1 academic center	24/61 classic DM; 3/23 ADM; 0/18 JDM	3/63	SIR DM: 7.44 women, 7.89 men PM and ADM: not statistically significant	Most frequent malignancies were breast, lung, pancreas, and colon Association between DM and cancer enhanced by its temporal relationship (<1 year) in 87.5% of cases
Limaye [23]	Cohort from South Australian myositis database	7/49	20/191	SIR DM: 2.17 ( $P = 0.09$ ) PM: 1.25 IBM: 1.37	Most frequent malignancies were lung and prostate Trend towards an increased SIR in DM, but no increased risk in PM or IBM
So [27]	Retrospective cohort study, Korean	23/98	2/53	SIR DM: 14.2 PM: 1.4	Most frequent malignancy was lung Independent factors associated with malignancies were older age, the presence of dysphagia, and the absence of ILD
Huang [28]	Yes, nationwide in Taiwan	136/1059	46/661	OR DM: 10.18 PM: 6.18 JDM: 16.16 (reticuloendothelial malignancies)	Most frequent malignancies were nasopharyngeal, lung, and breast Independent factors associated with malignancies were male gender and younger age (20s and 30s)



First author, ref.	Population-based?	Patients with CA in the DM/ADM group	Patients with CA in the PM group	Statistically different?	Comment(s)
Kuo [29]	Yes, nationwide in Taiwan	111/803	31/500	SIR DM: 5.36 PM: 1.80	Most frequent malignancies were nasopharyngeal and breast
Gerami [17]	Systematic review of case series/reports	29/197 All cases amyopathic			No control population. Mostly case reports
Azuma [30]	Retrospective review, 1 academic center in Japan	17/70 classic DM 3/15 ADM	3/51 PM	SIR 13.8 (DM/ADM/PM, not given separately for each subgroup)	Most frequent malignancy was gastric Independent factors associated with malignancies were older age, the presence of dysphagia, and the absence of ILD Both clinically ADM and classic DM were associated with similar high rates of malignancy in the cohort

ADM, amyopathic dermatomyositis; CA, cancer; CC, case-control; DM, dermatomyositis; CTD, connective tissue disease; IBM, inclusion body myositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; OR, odds ratio; PM, polymyositis; SIR, standardized incidence ratio.

**Table 63.2** Are there clinical or laboratory findings in dermatomyositis patients that suggest underlying malignancy?

First author, ref.	Population-based?	Patients with CA in DM/ADM group	Risk factor(s)	Effect (CA vs no CA group)	P/95% CI	Comments
Hill [18]	Yes	115/618	Age >45	Pos (SIR, 3.1)	CI, 2.6–3.7	
Stockton [20]	Yes	50/286	Age 45–74	Pos (SIR, 3.6)	CI, 2.0–5.9	
Airio [14]	Yes	63/311 (PM and DM)	Age >49	Pos (SIR, 8.2)	CI, 4.9–13	
Koh [34]	No	17/60 (PM and DM)	Arthralgia	Neg (48% vs 12%)	ND	Referrals from EMG lab or single hospital. Vasculitis, arthralgia not risk factors
			ILD	Neg (29% vs 12%)	ND	
			Mean age	Higher in CA group	<0.001	
Hochberg [35]	No	6/58 (PM and DM)	Mean age	No significant difference	ND	Statistics not given. Small number of patients. Raynaud's not a risk factor
			Dysphagia	Pos (67% vs 40%)		
			Arthralgia	Neg (0% vs 19%)		
			Vasculitis	Pos (33% vs 10%)		
Bohan [36]	No	13/110 (PM and DM)	Mean age	Higher in CA (62 y vs 47 y)	ND	Statistics not given. Dysphagia not a risk factor. Small number of patients
			Arthralgia	Neg (0% vs 23%)		
			Raynaud's	Neg (0% vs 13%)		
Pautas [37]	No (CC)	7/42 (PM and DM)	Age >65	Pos (OR of CA, 2.97)	0.24	
Marie [38]	No (CC)	16/79 (PM and DM)	Age >65	Pos (OR of CA, 9.35)	0.0001	
Henriksson [39]	No	7/70 (PM and DM)	Mean age	Higher in CA (57 y vs 52 y)	ND	
Duncan [40]	No	10/39	Mean age	Higher in CA (60 y vs 46 y)	0.02	Dysphagia, ESR not risk factors

*Continued*

Table 63.2 Continued

First author, ref.	Population-based?	Patients with CA in DM/ADM group	Risk factor(s)	Effect (CA vs no CA group)	P/95% CI	Comments
Chen [41]	No	18/105 (PM and DM)	Age >45	Pos (OR of CA, 9.1)	0.004	Multivariate analysis for age, sex, and ILD
			Male sex	Pos (OR of CA, 4.06)	0.04	
			ILD	Neg (OR of CA, 0.04)	<0.001	
			Elevated CPK	Pos (OR of CA, 5.16)	0.03	
			Arthralgia	Neg (OR of CA, 0.16)	0.08	
Feldman [42]	No	6/76 (PM and DM)	Cutaneous "vasculitis"	Pos (OR, 6.5)	0.09	Statistical trend only. Vasculitis only biopsied in one case
Hunger [43]	No	5/23	Cutaneous vasculitis	Pos (80% vs 17%)	<0.05	All cases biopsy-proven vasculitis as incidental finding on biopsy
Basset-Seguín [44]	No	13/32	Cutaneous necrosis	Pos (31% vs 5%)	0.05	Mean age not a significant risk factor
			Elevated ESR	Pos (54% vs 26%)	0.02	
Burnouf [45,46]	No (prospective)	8/26	Cutaneous necrosis	Pos (63% vs 11%)	0.01	Multivariate analysis
Mautner [47]	No	6/11	Cutaneous necrosis	Pos (100% vs 0%)	ND	Small study. Necrosis vaguely defined. Possible recall bias
Hidano [48]	No	171/569	ILD	Neg (4.7% vs 19%)	<0.01	Large number of cases. All diagnoses by questionnaire
Sparsa [49]	No	16/40 (PM and DM)	Elevated ESR	Pos (48% vs 25%)	0.008	Mean age, cutaneous necrosis, autoantibodies not risk factors
			Mean CPK	Higher in CA (2840 U/L vs 1346 U/L)	0.01	
			Raynaud's	Neg (0% vs 42%)	0.003	
			Constitutional symptoms	Pos (75% vs 29%)	0.009	
			Rapid-onset disease	Pos (63% vs 21%)	0.02	
Cox [50]	No	23/53	ILD	Neg (19% vs 46%)	0.1	UK hospital referral base. Vasculitis not a risk factor
			Mean age	Higher in CA (66y vs 53y)	0.001	
			Mean age	Higher in CA (56y vs 46y)	0.005	
			Cutaneous ulceration	Pos (44% vs 13%)	<0.05	
			Distal weakness	Pos (50% vs 6%)	0.007	
Ponyi [51]	No	16/84	Fever	Neg (0% vs 29%)	<0.05	Only malignancies <2y before or <5y after diagnosis of DM were considered. Dysphagia not a risk factor in this study
			Arthritis	Neg (25% vs 51%)	<0.05	
			Raynaud's	Neg (17% vs 26%)	0.038	
			ILD	Neg (19% vs 25%)	0.043	
			Mean CPK	Lower in CA (945 U/L vs 3612 U/L)	0.039	
Amerio [52]	No	14/59	Positive ANA	Neg (19% vs 39%)	<0.05	Multivariate analysis. Age, cutaneous necrosis, ANA, and muscle enzymes not risk factors
			Anti-Jo-1 antibody	Neg (0% vs 16%)	<0.05	
			ESR >35 mm/h	Pos (OR of CA, 197.5)	<0.05	
			ESR >35 mm/h	Pos (OR of CA, 197.5)	<0.05	
			ESR >35 mm/h	Pos (OR of CA, 197.5)	<0.05	
Marie [53]	No	28/156 (PM and DM)	ILD	Neg (7% vs 27%)	0.028	

First author, ref.	Population-based?	Patients with CA in DM/ADM group	Risk factor(s)	Effect (CA vs no CA group)	P/95% CI	Comments
Dourmishev [54]	No	12/50	Mean age	Higher in CA (59 y vs 49 y)	ND	No statistics available. Hospital-based study
			Poikiloderma	Pos (75% vs 32%)		
			Cutaneous ulceration	Pos (25% vs 2.7%)		
			Raynaud's	Neg (0% vs 17%)		
Nishikai [55]	No	12/36	Positive ANA	Neg (17% vs 54%)	<0.03	No data given on malignancies
Love [56]	No	13/92	Raynaud's	Neg (0% vs 40%)	ND	No statistics available. First study to link these protective effects into the "anti-synthetase syndrome"
			Arthritis	Neg (8% vs 55%)		
			Dyspnea	Neg (27% vs 59%)		
			ILD	Neg (0% vs 37%)		
			Positive ANA	Neg (31% vs 62%)		
			Anti-Ro/SSA	Neg (0% vs 11%)		
			Anti-U1RNP	Neg (0% vs 13%)		
			Anti-synthetase antibody	Neg (0% vs 33%)		
Trallero-Araguas [57]	No, cohort study	16/85 (PM and DM)	Anti-p155	Pos (OR of CA in DM, 23)	CI, 5.2–101	No statistical associations with peak CPK, dysphagia, ILD, or treatment response
			Shawl sign	Pos	$P < 0.01$	In DM, the PPV and NPV of anti-p155 for a diagnosis of CAM were 66.7% and 92%, respectively
Trallero-Araguas [58]	No, systematic review/meta-analysis	53/312	Anti-p155	Pos (OR of CA, 27.26)	CI, 6.59–112.82	In DM, the PPV and NPV of anti-p155 for a diagnosis of CAM were 58% and 95%, respectively
Hamaguchi [59]	No, multicenter cross-sectional	39/376	Anti-p155	Pos (10/17 with CA)	$P < 0.001$	Also found anti-CADM-140 to be associated with clinically ADM and rapidly progressive ILD
			Anti-Mi-2	Neg (0/9 with CA)	$P < 0.001$	Autoantibodies define distinct clinical subsets in DM and may be useful for predicting clinical outcomes
Fiorentino [62]	No	29/213	TIF-1 $\gamma$	Pos (OR, 1.6)	CI, 0.7–3.8; $P = 0.29$	Antibodies to either NXP-2 or TIF-1 $\gamma$ are present in most patients with cancer-associated dermatomyositis
			NXP-2	Pos (OR, 2.5)	CI, 0.9–6.7; $P = 0.069$	The absence of antibodies to either NXP-2 or TIF-1 $\gamma$ was strongly protective against cancer ( $P < 0.005$ )
			TIF-1 $\gamma$ or NXP-2	Pos (OR, 3.8)	CI, 1.3–10.8; $P = 0.013$	Stratification by sex showed that NXP-2 was specifically associated with malignancy in males (OR, 5.78; 95% CI, 1.35–24.7)

ADM, amyopathic dermatomyositis; ANA, antinuclear antibody; CA, cancer; CAM, cancer-associated myositis; CC, case-control; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; CPK, creatine phosphokinase; DM, dermatomyositis; EMG, electromyography; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; ND, no data; Neg, negative; OR, odds ratio; PM, polymyositis; Pos, positive; SIR, standardized incidence ratio.

above) are not fruitful in retrospective studies of patients with dermatomyositis [50,63–68].

On the other hand, other data support performing routine chest, abdomen, and pelvic computed tomography (CT) scans in adult patients presenting with dermatomyositis [18]. In one study, the positive result yield of a blind malignancy search was only 13%, but increased to 28% with blind chest/abdominal/pelvic CT scans [49]. The majority of these malignancies appeared to occur in patients experiencing cancer recurrence, suggesting increased surveillance in those with a known history of malignancy. In women, transvaginal pelvic ultrasound and mammography are also justified [49]. When comparing positron emission tomography/CT with conventional cancer screening (defined as chest and abdominal CT, mammography, pelvic ultrasound, gynecologic examination, and tumor marker analysis), the performances of both were comparable [69]. Another study demonstrated that sustained elevation of CA125 or CA19-9 are very specific findings in patients with cancer-associated dermatomyositis/polymyositis [70]. For patients with polymyositis, a chest radiograph and urinalysis should be performed at the time of diagnosis. Continued surveillance is necessary for patients with dermatomyositis for 3–5 years after diagnosis, but perhaps not for those with polymyositis [15,18,20]. However, what testing should be done beyond age-specific cancer screening remains somewhat unclear, and the clinician must formulate a plan in the absence of strong supporting data. Lastly, nasopharyngeal cancer is much more common among Asian patients in Southeast Asia, and a careful ear, nose, and throat evaluation is therefore warranted [29]. An additional study suggests that dermatomyositis patients residing outside of Southeast Asia, in areas such as the Mediterranean and North Africa, are also at increased risk of developing nasopharyngeal cancer, a risk not noted in Scandinavian and European studies on dermatomyositis-associated malignancies [71].

### Are there effective treatments for dermatomyositis?

The initial therapeutic approach to dermatomyositis depends on the presence of muscle and/or systemic disease. If present, systemic corticosteroids in relatively high doses are typically recommended as first-line therapy despite a lack of controlled studies supporting this approach. In addition, the early use of a corticosteroid-sparing agent is often proposed, with methotrexate, azathioprine, or mycophenolate mofetil being the most frequently suggested agents. In the absence of muscle and/or systemic involvement, there are no good data to support the use of systemic corticosteroids as a mainstay of therapy. Given that skin disease in dermatomyositis is often more refractory to treatment than the myositis, alternative agents are needed to avoid the side effects of systemic corticosteroids.

Do we know that these medications are effective, what the proper dosing should be, when a second-line agent should be introduced, which agent should be utilized, and what the likelihood of success is? Unfortunately, as is illustrated in Table 63.3 [36,72–119], the evidence available to answer these questions is poor. It is unclear whether the rate of remission is affected by systemic corticosteroids, whether they are used in high or low doses. In addition, there is little evidence regarding these therapeutic maneuvers for the treatment of cutaneous disease that might accompany dermatomyositis. Many reports do not specifically address skin disease response, and very few utilize the recently validated outcome measures for cutaneous disease.

Well-controlled randomized trials for this disease are lacking, and even the ones that have been conducted often lack power, or

have design flaws or potential biases. Many of the studies have included patients with cancer-associated myositis, a condition that is believed to respond less well than dermatomyositis without an associated malignancy. In addition, most studies mix dermatomyositis and polymyositis patients in their analyses, and it has become evident that these disorders differ in their pathogenesis and most likely have different responses to therapy.

### Current recommendations

It seems that there are no strong data that support the use of systemic corticosteroids in dermatomyositis, whether considering the muscle component, systemic disease such as pulmonary involvement, or the skin disease. Despite this lack of data, most authorities state that corticosteroids are a mainstay of therapy when myositis or systemic involvement is present. Therefore, it seems prudent to use corticosteroids for as short a period of time as is possible, substituting a steroid-sparing agent early in the course of treatment. Which of the agents to use is, in our view, dependent on the individual patient's co-morbidities and clinician's comfort level with the specific agent. For muscle disease, no high-quality trials support the use of a particular agent, with the possible exception of IVIG (see later). The addition of azathioprine to a corticosteroid regimen demonstrated a trend towards improvement [75]. Another study suggested that methotrexate and azathioprine do not appear to differ with respect to efficacy, although methotrexate was better tolerated [95].

Observations from individual case reports and small case series suggest that, for skin disease, hydroxychloroquine, methotrexate, and mycophenolate mofetil are effective corticosteroid-sparing agents. A retrospective series suggests that patients with dermatomyositis may have an increased risk of drug eruption to hydroxychloroquine [120]. Calcineurin inhibitors (such as ciclosporin and tacrolimus) also appear to be effective in skin disease, and may have a particular role.

IVIG has been the subject of a randomized controlled trial (RCT) and was found to be effective for both the muscle disease and the skin disease in patients with dermatomyositis refractory to corticosteroids and immunosuppressive agents. In this trial, 8 of 12 patients had “marked clearance” of skin disease as assessed through clinical photographs. Rituximab has recently been evaluated in an RCT; however, the primary outcome measure did not include any skin-specific measures, and no validated index to assess cutaneous disease response was utilized. Overall, the data regarding the use of rituximab specifically for cutaneous manifestations of dermatomyositis are limited.

What are the effects of treatments for juvenile dermatomyositis? This condition is complicated in two major ways. First, patients with juvenile dermatomyositis are more prone to calcinosis; and second, they may be permanently disabled by contractures. The results of retrospective case series suggest that the use of early “aggressive” therapy will limit the possibility of calcinosis [121,122]. Klein-Gitelman *et al.* [92] believe that high-dose intravenous pulsed methylprednisolone limits the risk and severity of calcinosis. However, adequate RCTs have not yet corroborated this belief. It does appear that, whatever the treatment, combination with physical therapy will prevent contractures from developing and that even if contractures occur, the use of physical therapy may improve the long-term disability. Once established, calcinosis may resolve spontaneously after a period of months to years; however, there are multiple individual case reports and some small series suggesting



Table 63.3 Treatments for patients with dermatomyositis.

First author (ref.)	Treatments compared/studied	Type of study	Outcome	Comments
<i>Corticosteroids</i>				
Winkelman [107]	CS therapy	Retrospective review of DM and PM  Primary end point: outcome of myositis	High-dose regimen (>50 mg/d) favored	No statistical analysis  Mixture of patients Identified some with an acute, fulminant course
Klein-Gitelman [92]	IVCS vs OCS	Retrospective comparison of 10	IVCS more costly, but more effective	Small group of patients
Bohan [36]	CS therapy	Retrospective of 124 patients	72% normalized CK levels	Mixture of patients
Nzeusseu [97]	Low-dose vs high-dose prednisolone (<0.5 vs >0.5 mg/kg/d)	Retrospective review of DM and PM ( $n = 25$ )	No difference in functional outcome	Vertebral fractures less common in low-dose group
Dawkins [81]	1 mg/kg/d prednisone with slow taper (over >2y)	Prospective DM (14 adult, 7 juvenile)	11/12 adults with normal strength/CPK 4/7 juveniles with normal strength/CPK	Cutaneous disease more difficult to treat
Van de Vlekkert [123]	High-dose pulsed oral dexamethasone vs daily high-dose prednisolone	Multicenter, double-blind RCT of patients with subacute onset myositis ( $n = 62$ ; 23 with DM)	No difference between treatment groups on composite score Side effects significantly less frequent in dexamethasone group	Mix of patients, fewer than half DM No statistically significant difference in skin changes on VAS (secondary outcome)
<i>Immunosuppressives</i>				
Mosca [96]	CS alone vs CS with immunosuppressive	Retrospective analysis	CS first-line therapy	
Bohan [36]	MTX for CS-resistant DM/PM Initial dose 10–15 mg/wk, raised to 30–60 mg/wk	Retrospective study. 25 patients (PM/DM)	16/25 improved strength	Minor, reversible toxicity
Ramanan [110]	CS alone vs CS with MTX	Retrospective study of juvenile DM	Addition of MTX resulted in decrease in total dose of CS, more rapid taper of CS. No difference in efficacy	Rapid CS taper only in MTX group, may have been tolerated in CS-only group
Bunch [75]	Prednisone 60 mg/d plus  AZA 2 mg/kg/d vs prednisone plus placebo	3-month DB-PC trial  16 patients with PM	No significant differences	
Miller [112]	CS+MTX vs CS+AZA	Double-blind, randomized ( $n = 28$ )	Equivalent efficacy on hand grip strength	MTX better tolerated than AZA
Villalba [104]	Oral weekly MTX and daily AZA vs i.v. MTX with leucovorin rescue	Randomized, open-label crossover study, 18 PM and 11 DM	ITT analysis showed trend in favor of oral combination	Toxicity slightly more common in i.v. group
Takada [101]	CYA (mean 156 mg/kg/d)	Retrospective analysis of 32 hospitals in Japan. 23 DM patients	Good response in 8/17 acute cases and 3/6 chronic cases	Only ILD measured as outcome. Unclear what parameters were measured
Kameda [90]	CYA (2–4 mg/kg/d) + CYT (10–30 mg/kg/d i.v.) + CS	Prospective study of 10 DM patients with severe ILD	5/10 survived. 5/10 died of respiratory failure	May compare favorably with historical controls (25% survival)
Heckmatt [88]	CYA (2.5–7.5 mg/kg/d)	Retrospective study of 14 patients with juvenile DM	Increased strength	
Danko [80]	CYA (2–3 mg/kg/d) (added to CS)	Retrospective of 10 DM patients, all refractory on CS $\pm$ AZA	“Remarkable” response in 6, “good” response in 4	Criteria for improvement unclear (muscle vs skin)
Maeda [111]	CYA	Retrospective study of 14 DM/PM patients in whom CS, MTX failed	9/14 “success” (still alive)	No mention of strength, skin response

Continued

Table 63.3 Continued

First author (ref.)	Treatments compared/studied	Type of study	Outcome	Comments
Grau [87]	CYA (5–10 mg/kg/d). No CS	Open-label study ( $n = 10$ ) 3 refractory, 7 new patients	Improvement in muscle function. Complete remission of skin disease in 9/10	Improvement more rapid than with historical CS + AZA. Oliguric renal failure in one patient. Only 10-month follow-up
Vencovsky [103]	CYA 3.0–3.5 mg/kg/d vs MTX 7.5–15.0 mg/wk with folic acid	Randomized, but not masked Mixture of PM and DM patients	Improvement equal. Trend towards superiority of MTX	Skin not evaluated
Wilkes [106]	Tacrolimus (0.075 mg/kg) b.i.d.	Retrospective study: 6 PM and 6 DM patients with interstitial lung disease	Significant improvement in strength and lung function	All had increased creatinine. Few with meaningful improvement in strength
Tausche [102]	MMF alone or with IVIG	Open-label, 4 patients	Three-quarters improved	One patient had cancer-associated DM
Majithia [94]	MMF+CS	Retrospective: 4 DM and 3 PM	Partial improvement of skin and muscle in all patients	One patient died of sepsis
Edge [82]	MMF alone or with other DMARD	Retrospective of 12 DM patients	Improvement of skin and strength in 10/12	1 recurrent breast cancer, 1 CNS lymphoma
Rowin [99] <sup>a</sup>	MMF+CS	Retrospective of 10 DM patients	Steroid-sparing in 6/7. Increased strength	3 opportunistic infections (1 patient died)
Riley [98]	I.v. CYT 0.5–1.0 mg/kg monthly alone or with DMARDs	Retrospective in 12 patients with refractory juvenile DM	10/10 response in muscle strength, 8/8 response in ulcerative skin disease	2 patients died. Significant infectious side effects. Response durable
Cronin [77]	I.v. CYT monthly	Retrospective ( $n = 6$ )	5/6 with “modest” improvement in strength	Serious infections (2) and death (11)
Sinoway [100]	Chlorambucil for DM	Open-label, 5 patients	Steroid-sparing	Assessment of myositis primarily
Adams [72]	Fludarabine 20 mg/m <sup>2</sup> for 3 d per month for 6 mos recalcitrant PM or DM	Open-label, 7 PM, 9 DM patients	Improved: 4 Unchanged: 7 Failures: 5	A subset of patients respond to this agent
<i>Plasmapheresis</i>				
Miller [95]	Plasma exchange or leukapheresis vs placebo	RCT of 39 patients with PM/DM	Equal effect to sham pheresis	Prior open-label trials had been positive
Cherin [76]	Plasma exchange	Retrospective, multicenter analysis of 24 PM and 33 DM patients in France	Significant improvement in acute myopathy only	PE given with albumin replacement in this study Must be combined with IVIG
Danieli [79]	CYA vs IVIG + CYA	Retrospective: PM ( $n = 8$ ) and DM ( $n = 12$ ). All on CS	Remission equal at 1 y, remission at 4 y more likely with CYA + IVIG	Combination well tolerated
Dalakas [78]	IVIG vs placebo for 3–6 months	DB-PC trial with crossover of 15	Statistically significant benefit for IVIG	Skin disease, strength, muscle biopsy
Al-Mayouf [73]	IVIG for JDM	Open-label, 18 JDM patients	Steroid-sparing	Small trial. Multiple regimens used
Gottfried [86]	IVIG for DM	Open-label trial with 19 patients (4 with cancer)	7 responders; nonresponders had severe skin and muscle disease, presence of MSA or cancer	IVIG monotherapy in some patients, used after immunosuppressive agents in some and with immunosuppressive agents in some
<i>Miscellaneous</i>				
Efthimiou [83]	Etanercept (+CS, IVIG)	Retrospective ( $n = 8$ ), PM and DM	6/7 patients improved with etanercept	1 splenic tumor. Only the nonresponder had a baseline normal CK
Muscle Study Group [124]	Etanercept plus prednisone vs prednisone alone (considered placebo group; each group was weaned off prednisone at a standardized schedule if tolerated)	Randomized, DB-PC pilot trial ( $n = 16$ ; 11 etanercept, 5 placebo)	No significant difference in adverse event rates Lower median average prednisone dose post week 24 in etanercept-treated group ( $P = 0.02$ )	5/11 etanercept-treated (vs 1/5 placebo-treated) developed worsening rash No significant difference in functional outcome

First author (ref.)	Treatments compared/studied	Type of study	Outcome	Comments
Dastmalchi [117]	Infliximab (5 mg/kg at weeks 0, 2, 6, and 14 × 4 mos)	Open-label trial (4 DM, 9 PM)	3/4 DM patients did not complete study (1 with severe erythema, 1 with worsening muscle disease, 1 with ovarian malignancy)	1 DM patient completed the study – did not improve based on muscle parameters
Hengstman [118]	Infliximab+MTX	Open-label trial (mixed DM and PM)	The few patients who reached the primary end point had improved muscle parameters	Terminated prematurely (low recruitment and high drop out from disease progression and infusion reactions)
Coyle [115]	Infliximab (5 mg/kg at weeks 0, 2, 6, and 14) vs placebo	Randomized, DB-PC trial with subsequent open-label crossover ( $n = 12$ ; only one with DM, 11 with PM)	7/12 on infliximab improved (vs 2/6 on placebo) Primary outcome met (improvement in MMT by 15% or more at 16wk)	Available in abstract form only Only one DM patient included
Levine [93]	Rituximab (375 mg/m <sup>2</sup> × 4) with or without other medication	Open-label in DM ( $n = 6$ )	All improved strength	4/6 relapsed with return of B cells Validated skin score not used
Chung [113]	Rituximab (1000 mg × 2)	Open-label in classic DM ( $n = 8$ ; 7 completed the study)	3/7 reached primary end point (at least 50% reduction in muscle deficit at week 24)	No improvement in skin scores using the validated DSSI
Oddis [114]	Rituximab (575 mg/m <sup>2</sup> for children with BSA ≤ 1.5 m <sup>2</sup> ; 750 mg/m <sup>2</sup> for patients with BSA > 1.5 m <sup>2</sup> , up to 1 g/infusion)	Multicenter RCT ( $n = 76$ DM, 76 PM, 48 JDM); randomized to: placebo at weeks 0, 1 and rituximab 1000 mg at weeks 8, 9; vs rituximab 1000 mg at weeks 0, 1 and placebo at weeks 8, 9	Did not reach primary end point (no difference in time to improvement in both groups) 161/195 (83%) had improvement in muscle disease Steroid-sparing effect was noted in both groups	The primary endpoint included 6 core measures of disease activity, none of which was skin specific No validated index to assess skin response was used
Wiesinger [105]	Physical training × 6 wk	Prospective, randomized study of 14 DM/PM patients	Improvement in muscle strength in treatment group	Suggests physical activity is safe for inflammatory myopathies
Takada [116]	Ecuzumab (humanized monoclonal Ab to CS) 8 mg/kg weekly × 5 wk followed by 2 × /wk for 2 additional doses vs placebo	Double-blind RCT ( $n = 13$ DM; 10 with ecuzumab, 3 with placebo)	No difference in adverse events MMT improved by 6% in treatment arm and 26% in placebo arm	Available in abstract form only
<i>Treatment of cutaneous disease of DM</i>				
Hollar [89]	Topical tacrolimus 0.1% ointment (all on CS±DMARD)	Open-label study ( $n = 6$ )	3/6 with acceptable improvement of rash	Not controlled
García-Doval [84]	Topical tacrolimus 0.1% ointment	Internally controlled (side-by-side comparison)	0/5 showed difference between treated and untreated sides	
Woo [108]	HCQ + CS (±MTX)	Retrospective ( $n = 7$ )	All patients had improvement of rash	No improvement in strength
Ang [74]	HCQ or CQ (±Q, ±DMARDs)	Retrospective ( $n = 17$ )	9/17 patients had “stabilization” of rash	Visual toxicity in 1 patient on CQ. Dyspigmentation in 3 on Q
Zieglschmid-Adams [109]	MTX for DM (7) or ADM (3), initial dose 7.5 or 9.2 mg/wk raised to 14.2 or 20 mg/wk for DM or ADM	Retrospective analysis	9/10 had improvement of skin disease	Mild, reversible toxicity in 7 patients Liver biopsy in 4 patients, 2 had hepatic fibrosis (grade IIIA)
Kasteler [91]	MTX for DM Eventual dose 2.5–30 mg/wk	Retrospective analysis 13 patients	CR – 4 PR – 9, steroid-sparing	Minimal toxicity
Hornung [119]	MTX for DM, dose 7.5–20 mg/wk	Retrospective analysis of 11 patients	8/11 with in skin disease (CDASI scores decreased from 15.7 to 6.4 ( $P < 0.01$ ) within 2–3 mos)	Responders had a more pronounced lymphocytic infiltrate in skin lesions
Gelber [85]	MMF for recalcitrant DM	Open-label, 4 patients	Steroid-sparing	

ADM, amyopathic dermatomyositis; AZA, azathioprine; CK, creatine kinase; CNS, central nervous system; CPK, creatine phosphokinase; CQ, chloroquine; CR, complete response; CS, corticosteroids; CYA, ciclosporin; CYT, cyclophosphamide; DB-PC, double-blind, placebo-controlled; DM, dermatomyositis; DMARD, disease-modifying anti-rheumatic drug; HCQ, hydroxychloroquine; i.v., intravenous; ILD, interstitial lung disease; ITT, intention-to-treat; IVCS, intravenous corticosteroids; IVIG, intravenous immunoglobulin; JDM, juvenile dermatomyositis; MMF, mycophenolate mofetil; MSA, myositis-specific antibodies; MTX, methotrexate; OCS, oral corticosteroids; PE, plasma exchange; PM, polymyositis; PR, partial response; Q, quinacrine; RCT, randomized controlled trial; VAS, visual analogue scale.

that various therapies – including warfarin, diltiazem, aluminum hydroxide, colchicine, minocycline, alendronate, pamidronate, probenecid, infliximab, IVIG, and hematopoietic stem cell transplantation – are variably effective in reversing the calcinosis. A multimodal approach to treating calcinosis is often warranted, including surgical excision of focal and disabling lesions.

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# Acquired subepidermal bullous diseases

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## Background

Acquired subepidermal bullous diseases are a heterogeneous group of acquired blistering diseases. They may affect patients' skin and mucous membranes to different extents and can lead to scar formation. We conform to the disease definition of existing international consensus statements in this discussion of bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP) [1,2]. BP is a non-scarring subepidermal blistering disease affecting mainly the skin; various autoantigens of the basement membrane zone (BMZ) mainly detected by immunoglobulin (Ig)G autoantibodies are recognized as being the targets. MMP is a (group of) subepidermal blistering disease(s) affecting mainly the mucous membranes, leading to scar formation in some patients. In MMP, various BMZ-antigens detected by IgG or IgA autoantibodies are associated with the disease. Autoantigens in the various acquired subepidermal bullous diseases may overlap considerably; this indicates that the autoantigen is not the only factor determining the clinical picture of the disease.

We will not discuss pemphigoid gestationis, a BP-like disease occurring in pregnancy; nor will we discuss linear IgA disease that shows considerable overlap with BP and MMP, considered as an entity by some because of the predominant IgA autoantibodies to various antigens and response to dapsone, or epidermolysis bullosa acquisita (EBA). All those "diseases" are very rare and show overlapping clinical as well as immunological features with BP and MMP [3–7].

## Bullous pemphigoid

### Definition

BP is an acquired non-scarring autoimmune subepidermal bullous disease characterized by tense blisters. Circulating IgG autoantibodies (rarely IgA, IgM, and IgE) typically bind to BP230 and BP180 (collagen XVII) antigens, which are components of the hemidesmosomal adhesion complex found in the BMZ of the skin. Direct antibody–antigen interaction, local activation of complement and release of cytokines lead to loss of dermoepidermal

adherence and formation of subepidermal blisters [8]. Blistering typically occurs in flexural sites although BP may be generalized or localized to one site such as the lower legs. Erosions and blisters occur on the mucous membranes, particularly the mouth, in about 50% of cases; however, they are usually not troublesome for the patient. Blister formation may be preceded for many months by pruritus, urticarial or eczematous rashes (Figure 64.1).

### Incidence/prevalence

BP is the most common autoimmune blistering disease in the West. In the UK [9], the reported incidence is 43 per million per year and 7–13 per million per year in other parts of Europe [10–12]. The mean age of onset is around 80 years. According to a Scottish study, there is no sex preponderance [13].

### Etiology

No clear etiological factors have been identified. There are anecdotal reports of BP being preceded by local cutaneous trauma. There is an association between BP and certain neurological diseases, such as cerebrovascular disease, dementia, and possibly Parkinson's disease, epilepsy, and multiple sclerosis [14–19]. BP is possibly triggered by drugs in certain patients [20]. There does not seem to be an increased risk of malignancy or other autoimmune diseases in patients with BP in Western countries compared with controls [13,21].

### Prognosis

BP is usually a self-limiting disease with a clinical course that may last from months to years. The majority of patients with BP will have disease remission within 5 years [22]. During the active stage, the disease is associated with significant morbidity and a mortality twice that of the general elderly population [9]. Older age at onset and frail general condition are poor prognostic factors. The mortality rate seems to be highest within the first 2 years of diagnosis [13,23]; according to the Scottish study, 48% died within 2 years (unrelated and related to BP or treatment); respiratory disease accounted for a higher than expected number of deaths [13]. Mortality during the first year is significantly higher in patients



Figure 64.1 Crusted erosions and large hemorrhagic bullae.

treated with high doses of systemic corticosteroids (prednisolone equivalent  $>40$  mg/day) [24]. Treatment should aim to control symptoms with minimum adverse effects where possible, as both treated and untreated BP shows a chronic relapsing course. Options are broadly divided into anti-inflammatory drugs, immunosuppressive or immunomodulating drugs, and procedures aiming to remove circulating pathogenic antibodies and inflammatory mediators.

### Aims of treatment

The aims of treatment are to achieve quick healing of skin and mucous membrane lesions and to improve quality of life with minimal adverse effects. The choice of treatment depends on an individual patient's circumstances, especially the severity and presence of co-morbidities

### Outcomes

- Rate of healing of blisters and suppression of new blister formation.
- Effect on quality of life.
- Duration of remission whilst on treatment and after cessation of treatment.
- Complications of disease.
- Adverse effects of treatment, including mortality.

### Methods of search

Randomized controlled trials (RCTs) were identified from searches of Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials, Medline, and Embase up to July 2012. All RCTs on interventions for BP confirmed by immunofluorescence studies were included.

A systematic review [25] of treatments for BP identified 10 RCTs, with a total of 1049 patients and nine ongoing trials: ACTRN12607000104459 (rituximab), NCT00286325 (rituximab), NCT00472030 (omalizumab), NCT00525616 (rituximab (Mabthéra)), NCT00802243 (leflunomide), NCT01571895 (Oral DF2156A), NCT00809822 and NCT01408550 (NPB-01 (intravenous Ig)), and ISRCTN13704604 (doxycycline versus prednisolone); the latter three are ongoing RCTs.

Detailed data on a completed 11th RCT comparing dapsone versus systemic steroid treatment in BP are not available [26].

## Questions

### What are the effects of systemic corticosteroids?

#### Benefits

Two small RCTs looked at the effects of systemic corticosteroids alone [27,28]. Dreno *et al.* compared biologically equivalent dosages of different corticosteroids: methylprednisolone, 1.17 mg/kg per day, and prednisolone methylsulphobenzoate, 1.16 mg/kg per day [27]. Morel and Guillaume compared different dosages of prednisolone: 0.75 mg/kg per day with 1.25 mg/kg per day [28]. Both trials found no statistical difference in effectiveness of treatment.

#### Harms

Higher doses of prednisolone were associated with more side effects, including infection, hepatic and renal impairment, cerebrovascular accident, hypertension, heart failure, and death.

#### Comment

Systemic corticosteroids are considered standard treatment for BP, although a placebo-controlled trial has not been carried out. Higher doses of corticosteroids are associated with increased morbidity and mortality.

### What are the effects of topical corticosteroids?

#### Benefits

We found two RCTs comparing very potent topical steroids versus prednisone [29,30].

In the first study [29], 341 patients with BP were stratified according to disease severity: moderate ( $\leq 10$  new blisters per day) or extensive ( $>10$  new blisters per day). Patients were randomly assigned to receive either topical clobetasol propionate cream (40 g b.i.d.) or oral prednisone (0.5 mg/kg per day for moderate disease and 1 mg/kg per day per for extensive disease). In the extensive disease group, those using topical steroids had a better survival rate at 1 year compared with those on oral steroids (76% vs 58%). This was consistent with the incidence of severe complications in the two extensive disease groups (29% for topical steroids vs 54% for oral steroids). The disease was controlled in 99% of the patients using topical steroids versus 91% of those on oral steroids at 3 weeks. In the moderate disease group, no significant differences were seen between the topical steroid and 0.5 mg/kg oral steroid groups in terms of overall survival, rate of disease control at 3 weeks, or the incidence of severe complications. In conclusion, disease control was similar comparing topical steroids with 1 mg/kg prednisone in the extensive group and 0.5 mg/kg prednisone in the moderate group. However, severe adverse effects and mortality were nearly double with 1 mg/kg prednisone compared with topical steroids; there was no difference with 0.5 mg/kg prednisone.

A second trial [30] investigated two different regimens of topical clobetasol propionate cream: 40 g cream per day versus a mild regimen of 10–30 g/day, depending on the body weight and severity of the disease. For moderate disease ( $\leq 10$  new blisters per day): 69 participants received 20 g/day if their body weight was  $\geq 45$  kg and 10 g/day if  $<45$  kg. For severe disease ( $>10$  new blisters per day): 90 participants received 30 g/day if their body weight was  $\geq 45$  kg and 20 g/day if  $<45$  kg. In the standard regimen, all participants received 40 g of the cream per day (moderate disease,  $n = 65$ ; severe disease,  $n = 88$ ).

In the mild regimen, 156/159 participants were controlled by day 21, and 150/153 in the standard regimen, which is not statistically significant; disease severity did not influence the results. There was



a 70% reduction in cumulative doses of corticosteroid used in the mild regimen. Eighty-nine patients in each group had severe adverse events; these were diabetes mellitus (34 vs 18), cardiovascular and neurovascular (35 vs 21), and severe infections (32 vs 27) in the standard and mild regimen groups respectively. There were also cutaneous side effects. In the mild regimen, 60/159 participants had died by year 1 (moderate disease, 19/69; severe disease, 41/90) and 58/153 in the standard regimen (moderate disease, 21/65; severe disease, 37/88). This was not statistically significant. However, an adjusted analysis (Cox model adjusted for age and Karnovsky score) showed a strong beneficial effect of the mild regimen in patients with moderate disease with an almost twofold reduction in death or life-threatening side effects, as compared with those treated with the standard regimen. In conclusion, the mild regimen was associated with less adverse effects over time.

### Harms

Skin infection, skin atrophy, and evidence of systemic absorption may be seen. There is a high risk of severe adverse reaction and death with 1 mg/kg per day prednisone.

### Comment

The two RCTs suggest the use of topical steroids as first-line for the treatment for both localized and mild disease [29,30]. Relatively few and mild side effects are associated with topical corticosteroid treatment in BP; however, their use in extensive disease may be limited by more side effects and practical factors (e.g., need for nursing input). Evidence suggests that 0.5 mg prednisone per kilogram per day is an appropriate dose for severe BP.

## Does combination treatment offer any advantage over corticosteroid monotherapy?

### Benefits

We found four nonblinded RCTs [31–34]. Burton *et al.* compared prednisolone, 30–80 mg/day, alone and in combination with azathioprine, 2.5 mg/kg per day. The addition of azathioprine resulted in a 45% reduction in prednisolone dose over a 3-year period [31]. Roujeau *et al.* compared prednisolone, 0.3 mg/kg per day, alone and in combination with plasma exchange. They found that less than half the total prednisolone dose was required in the plasma exchange group [32]. Disease control was achieved within weeks in both groups – in the plasma exchange group with a mean plus/minus standard deviation prednisolone dosage of  $0.52 \pm 0.28$  mg/kg per day and in the prednisolone-only group with  $0.97 \pm 0.33$  mg/kg per day. Guillaume *et al.* compared prednisolone 1 mg/kg per day alone or in combination with either azathioprine (100 mg for body weight <60 kg and 150 mg for body weight >60 kg) or plasma exchange [33]. This trial failed to confirm any benefit of combination therapy over prednisolone alone. Beissert *et al.* compared azathioprine (2.0 g/kg per day) to mycophenolate mofetil (1 g b.i.d.) as adjuncts to methylprednisolone (0.5 mg/kg per day). Remission was achieved in 100% of patients in both groups, but this trial included no steroid-only arm, so no conclusions can be drawn as to superiority of either adjunctive treatment over steroids alone [34]. Azathioprine was slightly faster to produce remission than mycophenolate (median 28.6 days compared with 42 days); however, relapse rates were similar. Finally, a small trial compared 15 patients with traditional Chinese medicine, “Jingui Shenqi Pill,” plus prednisone (0.5–1.0 mg/kg per day) with 15 patients on prednisone only (0.5–1.0 mg/kg per day) [35]. At 4 weeks, complete healing was achieved in one participant receiving the Jingui Shenqi

Pill and none in the prednisone group. Partial healing was achieved in 13 of 15 with Jingui Shenqi Pill treatment compared with 11 of 15 participants with prednisone-only treatment. None of the results were statistically significant.

### Harms

The addition of azathioprine and/or plasma exchange did not increase the incidence of side-effects; in fact, similar side-effect profiles were seen in the studies of Burton *et al.* and Roujeau *et al.* [31,32]. Guillaume *et al.* commented that most side effects could be attributed to corticosteroids, but details were not supplied [33]. Beissert *et al.* found a similar incidence of side effects with azathioprine and mycophenolate. Hepatotoxicity was documented in 6/37 patients treated with azathioprine, but more infections occurred with mycophenolate mofetil (MMF) [34].

### Comment

With the current available evidence the value of combination treatment remains doubtful.

## Are non-antibiotic properties of antimicrobials useful?

### Benefits

One small RCT compared prednisolone, 40–80 mg/day, with tetracycline, 2 g/day in four divided doses, plus nicotinamide, 1500 mg/day in three divided doses [36]. This trial suggested no statistically significant difference in treatment response.

### Harms

More serious side-effects (including death due to sepsis) were noted in the prednisolone group. One patient with established renal impairment in the tetracycline/nicotinamide group developed acute tubular necrosis; however, concomitant medications included aspirin and ibuprofen.

### Comments

This was a small trial of 18 patients, with an unclear method of randomization and a high drop-out rate.

An ongoing RCT (ISRCTN13704604) is investigating the effectiveness of doxycycline 200 mg/day versus prednisolone 0.5 mg/day in 256 patients (<http://www.controlled-trials.com/ISRCTN13704604>). The primary outcomes are effectiveness measured by a blinded blister count at week 6 and safety at 1 year; results are expected by October 2014.

Dapsone was compared with azathioprine in a small RCT of 54 patients with BP; 27 patients received methylprednisolone 0.5 mg/kg per day plus azathioprine 1.5–2.5 g/kg per day versus 27 patients receiving methylprednisolone 0.5 mg/kg per day plus dapsone 1.5 mg/kg. Preliminary results are presented; the main result was an earlier effect on healing of lesions in the dapsone group after 2.8 months versus 6 months in the azathioprine group; final results are awaited [26].

## What are the effects of immunoglobulins?

In studies NCT00809822 and NCT01408550, NPB-01 (intravenous Ig) therapy is compared with physiological saline for patients unresponsive to corticosteroids. Primary outcome measures are skin lesion area (percent), number of new blisters/day, pemphigoid activity score, anti-BP180 and -BP230 antibody titers, and steroid dose. These are randomized double-blind, placebo-controlled,

parallel assignment phase II and phase III studies. Data are not available.

### What are the effects of monoclonal antibodies?

Monoclonal antibody therapies could offer alternatives to long-term steroid use, or may permit the dose of steroids or immune-suppressive drugs to be reduced. Four of the ongoing studies are investigating the use of such biological agents. The use of rituximab as an adjuvant treatment in BP is being studied in ACTRN12607000104459, and the efficacy and tolerability of a single cycle of rituximab in the control of BP is being examined in NCT00525616. The safety and efficacy of omalizumab is being tested in NCT00472030, and the safety of treatment of BP in participants resistant to therapy with systemic corticosteroids, with rituximab plus systemic corticosteroids, in NCT00286325. Monoclonal antibody therapy may have a role to play in treatment of BP; however, it is not without adverse reactions, including infusion reactions, fever, neutropenia, chills, increased risk of infection, weakness, and fatigue.

#### Key points

- Few RCTs on systematic review of treatments for BP were identified.
- The available evidence is inadequate to allow confident recommendation of optimal treatment.
- Systemic steroids are the best established treatment for BP.
- Immunosuppressive and metabolic adverse effects occur and are dose dependent.
- Therefore, a less aggressive approach to therapy with low doses of corticosteroids may be sufficient for disease control and appears to be associated with less morbidity and mortality.
- Very potent topical steroids (clobetasol propionate) are an effective treatment for BP. They seem to have less serious adverse effects compared with 1 mg/kg of prednisone per day. However, their use in extensive disease may be limited by practical factors, and they may be associated with systemic absorption and adverse events. When feasible they should be considered for first-line treatment, especially in localized disease.
- Tetracyclines and nicotinamide may be effective; data of an ongoing, larger trial comparing doxycycline with prednisolone are expected late in 2014; this may clarify the effect on the anti-inflammatory effect of tetracyclines.
- The benefits of azathioprine, MMF, and plasma exchange are difficult to assess.

Strength of recommendation B.

## Mucous membrane pemphigoid

### Background

#### Definition

MMP is an acquired autoimmune bullous disease affecting primarily the mucous membranes and to a lesser extent the skin [2]. Following the international consensus in 2002, some patients previously considered to be linear IgA disease or EBA were reclassified as MMP (formerly cicatricial pemphigoid). Autoantibodies are directed against constituents of the hemidesmosomal adhesion complex of the skin and mucous membranes; the main autoantigens are BP180 and laminin-332 (laminin 5), and less commonly the  $\alpha 4$  and  $\beta 6$  integrins, collagen VII and other antigens. Autoantibody–autoantigen interaction leads to blister formation [2,37–39]. Direct immunofluorescence investigation of patients' skin or mucosa shows linear IgG, IgA, and C3 deposits at the der-

moepidermal junction, and indirect immunofluorescence of patients' serum may reveal circulating autoantibodies. Indirect immunofluorescence using salt-split skin may show binding to the roof (epidermis) in BP180-MMP or to the floor (dermis) in laminin 332-MMP of the artificial blister [38,39]. Scar formation is characteristic at many sites, though less commonly seen in the oral mucosa, and may result in blindness and respiratory obstruction.

### Incidence/prevalence

The incidence of MMP is estimated at 0.87 cases per million population per year in western Europe [40]. There is a slight female preponderance (1.5:1), and the elderly are more commonly affected.

### Etiology

The etiology is unknown; there are reports of drug-induced MMP [41].

### Prognosis

The course of MMP is variable; usually it is a very chronic disease [2]. Presentation may vary from stable oral involvement to rapidly progressive ocular disease despite immunosuppressive therapy.

### Aims of treatment

The aims of treatment are to achieve quick healing of mucosal and skin lesions, prevent scarring in the longer term induce disease remission, and to improve quality of life with minimal adverse effects.

### Relevant outcomes

- Rate of healing of blisters, cessation of blistering, and prevention of scarring.
- Effect on quality of life.
- Duration of remission after cessation of treatment.
- Complications of primary disease.
- Adverse effects of treatment, including mortality.

### Methods of search

RCTs of patients with MMP were identified from Medline/PubMed and Embase from their inception to July 2012. The Cochrane Skin Group Specialised (CSG) Register, the Cochrane Controlled Trials Register (CCTR: CENTRAL), [www.controlled-trials.com](http://www.controlled-trials.com), and [www.clinicaltrials.gov](http://www.clinicaltrials.gov) were last examined in August 2012. The bibliographies from identified studies were searched. However, because MMP is a rare disease we did not expect to find many RCTs and, therefore, also considered evidence from nonrandomized studies and case reports with diagnoses confirmed by immunofluorescence studies.

There is one systematic review of therapeutic interventions for MMP [42]. That review identified two small RCTs by Foster for the treatment of ocular MMP, but there were no placebo-controlled trials [43]. We identified one further RCT [44] and two ongoing trials.

## Questions

### What are the effects of combination therapy with cyclophosphamide?

#### Benefits

#### *Cyclophosphamide plus prednisolone versus prednisolone*

One double-blind RCT included 24 patients with bilateral ocular, stage III MMP (symblepharon formation). It compared pred-

nisolone (initially 1 mg/kg per day) alone versus cyclophosphamide (2 mg/kg per day) plus prednisolone [43, pp. 619–38, published data only]. Cyclophosphamide in combination with prednisolone was found to be effective in removing evidence of bilateral inflammation in stage III eye MMP in 12/12 participants. Only 5/12 participants had achieved disease control in the prednisolone-only group, and in all a recurrence of conjunctival inflammation occurred on tapering treatment (relative risk, 2.40; 95% confidence interval, 1.23–4.69).

#### ***Cyclophosphamide versus dapsone***

A second RCT included 40 patients with stage III ocular MMP [43, pp. 638–40, published and unpublished data]. It compared dapsone (2 mg/kg per day) with cyclophosphamide (2 mg/kg per day) in 40 patients with stage III ocular MMP. It is not clear, but both groups most likely had additional prednisolone, as in the above-mentioned trial [43, pp. 619–38, published data only]. Cyclophosphamide was found to be superior to dapsone in resolving severe inflammation of the eyes (20/20 vs 14/20; relative risk, 1.43; 95% confidence interval, 1.07–1.90). All six patients who did not improve after 3 months of dapsone treatment responded to cyclophosphamide.

#### **Harms**

No patients withdrew from systemic immunosuppression because of adverse effects. All of the patients in the prednisolone group experienced steroid-related adverse effects. Leukopenia was a routine finding in patients treated with cyclophosphamide; the dose was adjusted to achieve a white cell count of 2500–4000/ $\mu$ L; reversible hair loss and asymptomatic macrocytic anemia were common findings. Routine urinalysis detected microcytic hematuria in about 10% of patients taking cyclophosphamide. An alteration in timing of cyclophosphamide administration and increased fluid intake eliminated this potentially serious side effect (hemorrhagic cystitis). Male sterility may occur; there is a potential for development of malignancies (DNA damage).

#### **Comments**

With careful monitoring, systemic cyclophosphamide may pose fewer risks than long-term corticosteroid therapy for moderate and severe disease.

#### **What are the effects of sulfa-drugs?**

##### **Benefits**

There are no RCTs comparing the different sulfa-drugs. A small observational study (20 patients) describes that sulfapyridine may be superior to dapsone in moderate ocular MMP [45]. Another study suggests that sulfasalazine is effective in maintaining disease control in 6/9 patients with ocular MMP who have had previous dapsone-related side effects, although 2/6 required additional oral cyclophosphamide [46].

##### **Harms**

Dapsone must be given with care to patients with glucose-6-phosphate-dehydrogenase deficiency; some degree of anemia is common in most patients. There are potentially serious adverse effects in treatment with dapsone, like severe hemolytic anaemia, methemoglobinemia, agranulocytosis, neuropathy, and the dapsone syndrome (rash with fever and eosinophilia), which requires the immediate cessation of dapsone, because it may progress to exfoliative dermatitis and death.

#### **Comments**

Dapsone appears to be a reasonable first choice in patients with little inflammation and slowly progressive disease (the dose needs adjusting in glucose-6-phosphate dehydrogenase deficiency).

#### **Are non-antibiotic properties of antimicrobials useful?**

##### **Benefits**

Small noncontrolled studies (total of 25 patients) [47,48] indicate that minocycline (50–100 mg/day) or tetracycline (1 g/day) combined with nicotinamide (2.5–3 g/day) may be beneficial in oral disease.

##### **Harms**

Hyperpigmentation is a common side effect with minocycline.

##### **Comments**

RCTs are required to confirm the benefit of non-antibiotic properties of antimicrobials.

#### **What is the effect of intravenous immunoglobulin?**

##### **Benefits**

The use of intravenous Ig (IVIg) is described in one noncomparative case series of 10 patients with treatment-resistant progressive ocular MMP and showed resolution of conjunctivitis after 4–12 cycles of IVIg treatment (2–3 g/kg body weight per cycle every 2–6 weeks) [49]. A nonrandomized comparison between conventional immunosuppressive and IVIg therapies investigated eight patients in each group [50]. All patients received (various) immunosuppressive treatment as an initial treatment before treatment with IVIg.

##### **Harms**

There were no untoward side effects in these case series.

##### **Comment**

Comparative studies are needed. IVIg therapy is expensive [51].

#### **What is the effect of mycophenolate mofetil?**

##### **Benefits**

In a case series, treatment with MMF achieved complete control of inflammation in 70% of 18 treated patients with ocular pemphigoid (7% of a large cohort of different ocular inflammatory diseases) by 1 year [52]. In a series of 115 patients with ocular pemphigoid, patients were treated with various immunosuppressive drugs; cyclophosphamide therapy was more successful (69% success) than MMF (59% success) [53].

##### **Harms**

Lack of appetite, nausea, and mild diarrhea were common early side effects. Severe side effects resulting from immunosuppression were not noted in these series. In both studies, MMF had the least side effects among the immunosuppressive drugs used.

##### **Comment**

Larger comparative studies are needed to assess treatment efficacy of MMF.

#### **What is the effect of pentoxifylline?**

##### **Benefits**

The cytokine tumor-necrosis factor (TNF) has been detected in inflamed conjunctiva of MMP patients. The anti-inflammatory

(anti-TNF $\alpha$ ) effect of pentoxifylline was tested in 30 patients with ocular MMP [44]. Pulse steroids combined with cyclophosphamide in group A and intravenous pentoxifylline added to the combination in group B. Histopathological features and serum levels of TNF improved significantly. There were 0/9 relapses in group B after 18-month follow-up but 4/7 in group A.

## What is the effect of biologics?

### Benefits

Treatment with “biologics,” like TNF alpha receptor blocker (etanercept), infliximab, and anti-CD25 (daclizumab) which is now withdrawn, have been described in case reports. There are individual case reports and a small series of 25 patients with severe refractory MMP treated with anti-CD20 (rituximab). The series reported a response rate of 88%, with some patients requiring a second cycle to achieve remission [54].

### Harms

Severe side effects, including death, occurred in two patients when used concomitantly with glucocorticoids and immunosuppression.

### Comment

Further studies are needed.

### Ongoing trials

#### ISRCTN54055321: ex vivo expanded corneal limbal stem cell transplantation

This is a pilot clinical assessment of ex vivo expanded corneal limbal stem cell transplantation in patients with severe ocular surface diseases arising from limbal stem cell deficiency.

#### ISRCTN51714283: a randomized controlled trial of pulsed intravenous methylprednisolone for severe ocular pemphigoid

This tests the hypothesis that intravenous methylprednisolone induces more rapid control of ocular inflammation in patients with severe ocular pemphigoid.

### Key points

- The available evidence is inadequate for confident recommendation of optimal treatment.
  - Dapsone combined with systemic corticosteroids may be helpful in the management of mild ocular MMP with modest inflammation.
  - Cyclophosphamide combined with systemic corticosteroids appears to suppress inflammation and scarring in moderate to severe ocular MMP.
  - Antimicrobials, MMF, IVIGs, and rituximab are of unknown benefit in the management of MMP. RCTs are needed to determine their efficacy.
- Strength of recommendation B

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# Pemphigus

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## Background

### Definition

Pemphigus is an intra-epidermal autoimmune blistering disease involving the skin and mucous membranes. Pemphigus is conventionally divided into three distinct subtypes: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Pemphigus vulgaris is characterized by blisters affecting both oral and cutaneous surfaces, whereas patients with pemphigus foliaceus have only cutaneous involvement (Figure 65.1). Patients with paraneoplastic pemphigus have striking mucous membrane disease, as well as a polymorphous skin eruption, with a poor prognosis. In this chapter we will exclusively address pemphigus vulgaris and foliaceus.

### Epidemiology

The incidence of pemphigus has been estimated at approximately 1 in 1 000 000 to 1 in 100 000 per year, depending on the population in question [1].

### Etiology

As is the case with other autoimmune diseases, the exact pathophysiological mechanism that causes immune dysregulation in pemphigus is unknown. Pemphigus is a T-cell-driven autoantibody-mediated disease, with T cells reacting to specific antigenic adhesion proteins in the skin. The production of autoantibodies to intercellular proteins in the epidermis, along with various inflammatory mediators, is believed to directly elicit acantholysis. The clinical phenotype of pemphigus is defined by the specific profile of autoantibodies. Patients with mucosal-dominant pemphigus vulgaris have only antidesmoglein 3 immunoglobulin (Ig)G autoantibodies. Patients with mucocutaneous pemphigus vulgaris have both antidesmoglein 3 and antidesmoglein 1 autoantibodies. Patients with pemphigus foliaceus, who have only skin lesions, have antidesmoglein 1 antibodies [1].

### Prognosis

The mortality of pemphigus decreased dramatically after corticosteroids were introduced as therapy in the 1950s. Before that time, the mortality was approximately 70% and usually resulted from sepsis [2]. With corticosteroids and adjuvant therapy, the mortality is now approximately 6%, with most deaths being related to side effects of therapy [3].

### Diagnosis

Diagnosis is based on four measures:

- *Clinical features:* oral ulcers, flaccid blisters, or erosions with scale.
- *Histological features:* acantholysis with loss of coherence between epidermal cells.
- *Immunofluorescence:* detection of autoantibodies either in a biopsy specimen (direct) or in the patient's serum (indirect) in an intercellular pattern with IgG and C3.
- *The enzyme-linked immunosorbent assay:* antidesmoglein 1 or 3 antibodies – antibody titers may correlate with disease activity [4].

### Aims of treatment

The main aims of treatment in pemphigus are to suppress new blister formation and promote the healing of old lesions whilst minimizing the side effects of treatment.

### Relevant outcomes

Interpretation of evidence is complicated by the lack of uniform outcome measures. Outcomes regarding disease control include prevention of new blister formation, healing of old lesions, and the time required to achieve disease control. In the longer term, the proportion of patients able to discontinue treatment and the proportion of patients who relapse are important. The safety of treat-



**Figure 65.1** Patient with extensive erosions and flaccid bullae due to pemphigus vulgaris.

ments is especially important, as the major morbidity is derived from complications of treatment. Cumulative steroid dose is often measured as a surrogate for steroid-induced adverse events. Autoantibody titers are reported to correlate with disease activity. Patient-based measures, including quality of life, should also be considered. An international consensus document regarding relevant outcomes and definitions of response has been published [5]. Two validated severity scores have also now been published, which will aid meta-analysis in the future [6,7].

### Search strategy

Articles were identified from the Cochrane Central Register of Controlled Trials (Central), Medline, and Embase, using the Cochrane Collaboration's highly sensitive search strategy.

### Study selection criteria

We focused our analysis on randomized controlled trials (RCTs), but also included nonrandomized trials and large case series when RCTs were lacking.

## Questions

### What is the optimal dosing strategy for corticosteroids in newly diagnosed patients?

Corticosteroids are firmly established as the mainstay of treatment for pemphigus. Their introduction in the 1950s was associated with a dramatic decrease in mortality [8–10]. Initially, very high doses were employed, but these doses were associated with significant adverse events, and the rationale for high-dose regimens has been questioned [11–13].

In the only RCT to address steroid-dosing regimens, Ratnam *et al.* compared the efficacy of different prednisolone doses [14]. Twenty-two previously untreated patients with severe disease (>50% of the body surface area affected) were randomly assigned to “high-dose” (120–150 mg/day;  $n = 11$ ) or “low-dose” (30–60 mg/day;  $n = 11$ ) prednisolone. Patients also received adjuvant therapy with methotrexate or cyclophosphamide when steroids were tapered below 20 mg/day. Patients were followed for 5 years. All patients were seronegative for pemphigus autoantibodies after 3

months of treatment (initial titers ranged from 1:40 to 1:160). All patients in both groups had resolution of blister formation. There was no difference between the duration of prednisolone therapy required to control disease (average 19 vs 24 days). There was no difference in the number of relapses between groups, or in the time to relapse. Steroid-related complications occurred in both groups, with a trend towards more complications in the high-dose group. Therefore, this trial suggested that a “high-dose” regimen offered no advantage over a “low-dose” regimen.

Fernandes and Perez reported a nonrandomized controlled trial involving 71 patients (41 with pemphigus vulgaris, 30 with pemphigus foliaceus) [15]. Patients were allocated to groups receiving 1 mg/kg per day ( $n = 34$ ) or 2 mg/kg per day ( $n = 37$ ) prednisone, according to baseline disease severity. No adjuvant agents were given, and steroids were tapered after 4–6 weeks. Patients were followed for 5 years. Suppression of blister formation was similar in the two groups, with 24 of 34 patients on low-dose treatment and 27 of 37 patients on high-dose treatment responding to therapy. Two patients in the low-dose group and four in the high-dose group died. There was a significant difference in the number of adverse events, in particular infection, with 16 infections reported in the low-dose group and 48 in the high-dose group. Although the lack of randomization in this study detracts from the validity of the results, it suggests that high doses of steroid are no more effective and are associated with higher morbidity.

In summary, the evidence indicates that lower dosage steroid regimens ( $\leq 1$  mg/kg per day) have equivalent efficacy in inducing disease control and that higher dosage regimens are associated with increased morbidity.

### Does pulsed corticosteroid therapy increase efficacy or reduce morbidity?

Pulsed therapy is based on the rationale that short-term high-dose steroid may achieve more rapid control of disease and decrease cumulative steroid dose, thus reducing complications resulting from long-term usage. There has been one RCT, one nonrandomized controlled trial, and four case series reporting on the use of pulsed corticosteroid therapy.

Mentink *et al.* reported an RCT including 20 pemphigus vulgaris patients with new disease or new disease activity randomized to oral dexamethasone 300 mg pulses 3 days per month ( $n = 11$ ) or placebo ( $n = 9$ ) [16]. Both treatment groups also received prednisolone 80 mg/day, tapered over 19 weeks, and azathioprine 3 mg/kg per day. Monthly pulses were continued until prednisolone was tapered to zero, and the patients were followed for 1 year. Eight of the 11 patients with pulsed dexamethasone and all nine of the patients on placebo were able to discontinue all steroids. There were no differences in the time to remission, duration of remission, or relapse rate. The mean cumulative steroid dose was higher in the pulsed group. Adverse events occurred more commonly in the pulsed group, and three of nine patients withdrew due to side effects. Adverse events with pulsed therapy included viral hepatitis, muscle weakness, cognitive problems, and weight gain.

Femiano *et al.* reported an open nonrandomized controlled trial of 20 patients with new-onset pemphigus vulgaris [17]. The patients were treated with a tapering schedule of prednisone 125 mg/day ( $n = 10$ ) or intravenous betamethasone 20 mg/day for 4 days/month and prednisone 50 mg/day. There was no difference in the time to achieve disease control (30 vs 25 days). Adverse events were reported less commonly in the pulsed group.

A study of pulsed dexamethasone and cyclophosphamide versus pulsed cyclophosphamide and prednisolone, discussed later, also did not demonstrate a benefit for pulsed dexamethasone [18].

These controlled trials did not demonstrate an additional benefit for pulsed corticosteroids, and were associated with more severe side effects. However, patients in these controlled trials were predominantly newly diagnosed, and as pemphigus is steroid responsive overall, a difference would not be expected without selection for a subgroup of patients with severe or refractory disease. The role for pulsed corticosteroid therapy in patients with severe or refractory disease is not clear.

### **Are immunosuppressive drugs (azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate) in addition to corticosteroids beneficial in improving efficacy or reducing morbidity?**

Immunosuppressive medications are widely used owing to their theoretical advantage of improving efficacy while reducing steroid-induced complications. These agents are slow acting, so their primary role is in maintenance therapy rather than in inducing remission. There have been seven RCTs of immunosuppressants, including a four-arm trial comparing prednisolone alone versus adjuvant azathioprine, cyclophosphamide, and mycophenolate mofetil in 120 patients [19]. In this open-label study, newly diagnosed cases were randomized to prednisolone alone at a starting dose of 2 mg/kg with a predetermined tapering schedule or prednisolone plus immunosuppressants. Dosage protocols consisted of azathioprine 2.5 mg/kg for 2 months, then 50 mg/day; mycophenolate mofetil 2 g/day for 12 months; or pulsed cyclophosphamide 100 mg/month for 6 months, then bimonthly for 6 months. Primary outcomes were cumulative glucocorticoid dose, response, recurrence rate, and adverse events. Overall, there was a difference in cumulative steroid dosage (analysis of variance  $P = 0.047$ ).

#### **Azathioprine**

Adjuvant azathioprine ( $n = 30$ ) was compared with prednisolone alone ( $n = 30$ ) in Chams-Davatchi *et al.*'s multi-arm study [19]. The mean cumulative steroid dosage was significantly reduced in the azathioprine relative to the prednisolone arm (7712 mg vs 11 631 mg,  $P = 0.047$ ). The clinical response rate was similar at 24/30 versus 23/30. One patient had a treatment failure, and two patients demonstrated significant elevation of liver enzymes in the azathioprine group.

Akhtar and Hasan reported a nonrandomized controlled trial in 72 pemphigus vulgaris patients, comparing prednisolone ( $n = 40$ ), prednisolone plus azathioprine ( $n = 15$ ), and betamethasone-cyclophosphamide pulse therapy ( $n = 17$ ) [20]. The regimen consisted of prednisolone 30–120 mg/day on a tapering schedule, alone or in combination with azathioprine 100–150 mg/day. Treatment with azathioprine was more effective with regard to the proportion of patients achieving disease control (11/15 vs 13/40; response difference, 0.41; 95% confidence interval [CI], 0.14–0.68; number needed to treat, 3; 95% CI, 2–8). The frequency of relapses and the incidence of complications were lower in the azathioprine group. Eight of the 40 patients in the prednisolone arm died, compared with one of the 15 in the azathioprine arm.

Chaidemenos *et al.* reported a retrospective chart review comparing outcomes of 36 patients with oral pemphigus vulgaris treated with oral prednisolone alone, or prednisolone plus azathioprine. They noted similar overall response rates, but with lower

cumulative steroid dosages and adverse events in the azathioprine group [21].

#### **Cyclophosphamide**

Adjuvant pulsed cyclophosphamide ( $n = 30$ ) was compared with prednisone alone ( $n = 30$ ) in Chams-Davatchi *et al.*'s multi-arm study [19]. The mean cumulative steroid dosage was significantly reduced at 8276 mg versus 11 631 mg. The clinical response rate was similar at 22/30 versus 23/30. Adverse events in the cyclophosphamide group were not reported separately. Six patients in the cyclophosphamide arm were lost to follow-up and one excluded due to poor compliance.

Sethy *et al.* reported an open RCT of 28 patients with pemphigus vulgaris with active disease comparing two dosage regimens of cyclophosphamide [18]. Interventions included dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide (DCP + C) versus cyclophosphamide pulse and daily oral prednisolone (CP + P). The regimen of DCP + C consisted of pulsed dexamethasone 100 mg daily for 3 days, plus intravenous cyclophosphamide 500 mg on day 1 and oral cyclophosphamide 50 mg daily; pulses were repeated monthly for 12 months and oral prednisone 0.5–0.75 mg/kg per day was added if required. CP + P consisted of pulsed monthly cyclophosphamide 15 mg/kg per day and oral prednisolone at a starting dosage of 1.5 mg/kg per day on a predetermined tapering schedule. The primary outcome was time to remission. Results demonstrated earlier mean time to remission in the CP + P group of 8.4 weeks versus 13 weeks in the DCP + C group. Efficacy parameters and relapse rates were similar. There were increased acute steroid-related adverse events in the DCP + C group and increased long-term steroid-related adverse events in the CP + P group.

Chrysomallis *et al.* conducted an RCT of prednisone, cyclophosphamide, and cyclosporine [22]. Twenty-eight patients with newly diagnosed pemphigus vulgaris restricted to the oral cavity were randomized to prednisone equivalent 40 mg daily ( $n = 10$ ), alone or in combination with either cyclophosphamide 100 mg/day ( $n = 10$ ), or cyclosporine 5 mg/kg per day ( $n = 8$ ). All patients were followed for 5 years. There was no significant difference in the duration of treatment required to achieve disease control between cyclophosphamide and prednisone alone (mean 24 vs 28 days), relapse rate, or disease control at 5 years. Adverse events were mild, although the incidence of complications was higher with combination treatments.

A nonrandomized controlled trial comparing prednisolone, prednisolone plus azathioprine, and betamethasone-cyclophosphamide is described above [20]. Treatment was considered to have failed in 12 of the 17 patients in the pulsed cyclophosphamide arm, and the patients required additional steroids. An increased susceptibility to infection was also seen in the cyclophosphamide group and four of the 17 patients died.

In summary, cyclophosphamide appears to have a steroid-sparing benefit, although the potential adverse events are considerable. Cyclophosphamide may have a role in certain cases of refractory disease.

#### **Cyclosporine**

There have been two RCTs addressing cyclosporine in pemphigus and a number of case series. Ioannides *et al.* reported an open-label RCT of 33 patients with newly diagnosed pemphigus (29 with pemphigus vulgaris and four with pemphigus foliaceus) [23]. Treatment regimens included prednisolone 1 mg/kg ( $n = 17$ ) or



prednisolone 1 mg/kg plus cyclosporine 5 mg/kg ( $n = 16$ ), tapered and discontinued according to a standardized protocol, with follow-up of 4–6 years. There were no differences in any of the variables used to measure the response to treatment (mean 17 days in both groups), the proportion of patients able to taper steroids below 15 mg/day (12/17 and 12/16 at 12 months), the proportion of patients able to stop treatment (5/17 and 4/16 at 12 months), the time to achieve remission, or treatment failure (2/17 and 1/16). Complications were more common among patients who received combination therapy.

Similar results were reported in an RCT of cyclosporine by Chrysomallis *et al.* described above in the cyclophosphamide section [22]. There was no benefit from cyclosporine with regard to the time needed to achieve disease control, the proportion of patients responding to treatment, or the relapse rate. The incidence of adverse events, particularly hypertrichosis and renal impairment, was higher in the cyclosporine group.

From the available evidence, adjunctive cyclosporine does not appear to be beneficial in pemphigus. Efficacy does not appear to be greater than with steroids alone, and adverse events are more frequent.

### Methotrexate

No controlled trials have tested the efficacy of methotrexate in pemphigus. In a series of nine pemphigus vulgaris patients, all of whom had had been treated unsuccessfully with another adjuvant agent, Smith and Bystryn reported the use of methotrexate at dosages of 10.0–17.5 mg/week in combination with prednisone [24]. Once the disease was controlled, steroids were rapidly tapered, and six of the nine patients were able to discontinue steroids within 6 months. Adverse events were mild and included nausea and mild elevation of transaminases.

Mashkileysen and Mashkileysen reported 53 patients with pemphigus vulgaris who were treated with prednisone 60–200 mg/day and methotrexate 25–50 mg/week [25]. Treatment was reported as “effective” in 42 of the 53 patients and “ineffective” in nine, and two patients withdrew due to adverse events. There were no changes in liver enzymes, and liver biopsies performed after every 1.5 g cumulative methotrexate were unremarkable. A steroid-sparing effect was seen. The most common adverse effect was infection. Twenty-eight of 185 patients in this case series died, but the number of these who were receiving methotrexate was not reported.

There is insufficient evidence to draw conclusions regarding the role of adjuvant methotrexate in pemphigus.

### Mycophenolate mofetil

Adjuvant mycophenolate mofetil ( $n = 30$ ) was compared with prednisolone alone ( $n = 30$ ) in Chams-Davatchi *et al.*'s multi-arm study [19]. The mean cumulative steroid dosage was lower in the mycophenolate mofetil arm, at 9798 mg versus 11 631 mg, although the difference was not statistically significant. The clinical response rate was similar at 21/30 versus 23/30.

Beissert *et al.* reported a placebo-controlled RCT adjuvant mycophenolate in 96 patients with pemphigus vulgaris [26]. The interventions included mycophenolate mofetil at a dose of 2–3 g daily versus placebo. All patient also received prednisolone 1–2 mg/kg tapered according to a predetermined schedule. The primary outcome measure was response to treatment. Results demonstrated similar response rates of 40/58 (mycophenolate mofetil) versus

23/36 (placebo). The MMF group demonstrated a more rapid response to treatment (24.1 weeks vs 31.3 weeks;  $P = 0.0152$ ) and delayed time to relapse. The cumulative steroid dose was decreased at 7617.5 mg versus 8727.5 mg. There were fewer serious adverse events in the mycophenolate mofetil group, although the rate of infections was increased.

### Summary

The study by Chams-Davatchi *et al.* demonstrates a steroid-sparing benefit of adjuvant immunosuppressive agents, although no difference was observed in clinical end points. Differences in cumulative steroid dosage are a surrogate end point.

### Which immunosuppressive agent is most effective?

#### Azathioprine versus mycophenolate mofetil

Beissert *et al.* reported an RCT comparing azathioprine and mycophenolate mofetil in 40 patients with pemphigus vulgaris and pemphigus foliaceus [27]. Interventions included azathioprine 2 mg/kg versus mycophenolate mofetil 1 g b.i.d. All patients received a uniform dose of methylprednisolone. Results demonstrated similar time to response and remission rates with 13/18 in the azathioprine group and 20/21 in the mycophenolate group. There was no difference in duration of remission. Cumulative steroid dosage was similar in both groups. Adverse events were similar in both groups.

In the multi-arm trial by Chams-Davatchi *et al.* described earlier, the cumulative steroid dosage was lower in the azathioprine group than in the mycophenolate group (7712 mg vs 9798 mg;  $P = 0.007$ ) [19]. Clinical response rates were similar.

#### Azathioprine versus cyclophosphamide

Rose *et al.* conducted an open RCT comparing intravenous dexamethasone–cyclophosphamide and oral methylprednisolone–azathioprine [28]. Twenty-two patients with newly diagnosed disease (16 with pemphigus vulgaris and six with pemphigus foliaceus) were enrolled. The patients were randomly assigned to methylprednisolone 2 mg/kg plus azathioprine 2.0–2.5 mg/kg ( $n = 11$ ) or intravenous dexamethasone 100 mg/day for 3 days and cyclophosphamide 500 mg on day 1, plus oral cyclophosphamide 50 mg/day ( $n = 11$ ). The dexamethasone–cyclophosphamide pulse was administered every 2–4 weeks at increasing intervals. At 24 months, five of the 11 patients in the methylprednisolone–azathioprine group and one of the 11 in the dexamethasone–cyclophosphamide group had controlled disease on treatment; three of the 11 in each group were in remission and had stopped therapy; and one in the methylprednisolone–azathioprine group and six in the dexamethasone–cyclophosphamide group had had progression of disease. Patients who progressed on dexamethasone–cyclophosphamide were subsequently treated with the methylprednisolone–azathioprine regimen, and all improved. One patient in the methylprednisolone–azathioprine group withdrew due to generalized herpes simplex virus infection. Adverse events were reported more commonly in the methylprednisolone–azathioprine group.

In the multi-arm trial by Chams-Davatchi *et al.* described earlier, cumulative steroid dosages and clinical response rates were similar in azathioprine and cyclophosphamide groups [19].

Akhtar and Hasan reported a nonrandomized controlled trial comparing prednisolone ( $n = 40$ ), prednisolone plus azathioprine ( $n = 15$ ) and betamethasone–cyclophosphamide pulse therapy ( $n = 17$ ) in pemphigus vulgaris [20]. This trial was described in part in the section on azathioprine above. The regimen consisted

of pulsed intravenous betamethasone 100 mg/day for 3 days and cyclophosphamide 500 mg on day 1, plus cyclophosphamide 50 mg orally daily. Treatment was considered to have failed in 12 of the 17 patients in the pulsed cyclophosphamide arm, and the patients required additional steroids. An increased susceptibility to infection was seen in the betamethasone–cyclophosphamide group in comparison with other arms, and four of the 17 patients died.

### Cyclosporine versus cyclophosphamide

In the paper by Chrysomallis *et al.* described earlier, there was no significant difference in the duration of treatment required to achieve disease control between cyclosporine and cyclophosphamide (mean 25 vs 24 days), the relapse rate, or the remission rate at 5 years [22].

### Mycophenolate versus cyclophosphamide

In the multi-arm trial by Chams-Davatchi *et al.* described earlier, cumulative steroid dosages and clinical response rates were similar in the cyclophosphamide and mycophenolate groups [19].

### Does immunomodulatory therapy (i.e., plasmapheresis or intravenous immunoglobulin) improve efficacy or reduce morbidity in patients with severe or recalcitrant pemphigus?

Immunomodulatory therapies are appealing, as they target the antibodies that are directly pathogenic in pemphigus. However, because these agents/modalities are more invasive and substantially more costly, these modalities are usually reserved for patients with severe recalcitrant disease.

#### Plasmapheresis

Guillaume *et al.* randomly assigned 40 previously untreated patients with pemphigus vulgaris and foliaceus to prednisolone alone (0.5–2.0 mg/kg per day;  $n = 18$ ) or prednisolone plus 10 large-volume plasma exchanges (55 mL/kg per exchange) over 4 weeks ( $n = 22$ ) [29]. There were no differences between the two groups with respect to clinical improvement, cumulative steroid dose, or serum autoantibody titers. Eight patients (four in each group) did not achieve disease control. Four patients, all in the plasmapheresis group, died of sepsis or thromboembolism. This study suggests that plasmapheresis in association with steroids is not effective in the treatment of pemphigus. Other authors have argued that the poor efficacy of plasmapheresis in this trial is related to various aspects of the trial protocol [30,31]. Nevertheless, the high mortality rate in the plasmapheresis arm is concerning.

Eight previous case series demonstrated more promising results. The role of plasmapheresis in pemphigus is unclear. The lack of benefit and high mortality rate in this study suggest that plasmapheresis should not be recommended in patients with new-onset disease. However, the role of plasmapheresis in patients with severe recalcitrant disease is unclear.

#### Immunoadsorption

Immunoadsorption is similar to plasmapheresis, but immunoglobulins are specifically removed from the circulation. There are three case series describing immunoadsorption in pemphigus.

Lüftl *et al.* conducted a prospective case series on protein A immunoadsorption, including nine patients (seven with pemphigus vulgaris and two with pemphigus foliaceus) [32]. The treatment regimen consisted of two cycles of immunoadsorption separated by 48 h, given with a pulse of prednisolone. Patients were continued on methylprednisolone 0.5 mg/kg per day and on preexisting adju-

vant medication. All of the patients showed clinical improvement, allowing reduction of steroid doses. Antibody titers decreased by 30% after a single treatment, and IgG was preferentially eliminated in comparison with other plasma proteins. One patient had an anaphylactic reaction and immunoadsorption was discontinued.

Schmidt *et al.* described the use of immunoadsorption in five patients (four with pemphigus vulgaris and one with pemphigus foliaceus) [33]. The patients were treated with 19 cycles of immunoadsorption over 41 weeks, in addition to 0.5 mg/kg methylprednisolone, which was gradually tapered. Pulsed cyclophosphamide and dexamethasone for administered with the initial cycle of immunoadsorption. Clinical improvement was seen within 2 weeks, and the patients became lesion free in 3–21 weeks. One patient relapsed, but responded to a second induction cycle. A steroid-sparing effect was seen. Antibody titers decreased by an average of 75% at 1 month. Adverse events reported included deep vein thrombosis, bradycardia and hypertension, symptomatic hypocalcemia, and difficulty with venous access.

Shimanovich *et al.* reported a prospective case series of nine patients with pemphigus vulgaris treated with immunoadsorption, in combination with methylprednisolone 2 mg/kg and adjuvant azathioprine or mycophenolate [34]. All patients demonstrated rapid initial clinical response, with decreased circulating antibody levels. The therapy was well tolerated.

Immunoadsorption appears to be an effective treatment in inducing rapid clinical improvement, associated with decreased antibody titers and a steroid-sparing effect.

#### Intravenous immunoglobulin

There has been one RCT including 61 participants (40 pemphigus vulgaris, 21 pemphigus foliaceus) examining a single cycle of two dosage regimens of intravenous Ig against placebo [35]. Included patients had active disease, uncontrolled on prednisolone doses of 20 mg/day or more. Fourteen of the 61 patients were on concomitant immunosuppressants. The primary outcome measures was “time to escape from protocol,” defined as the time until additional therapy was required due to lack of response or disease worsening. Hazard ratios were not reported; however, there was a difference in the number of patients remaining “in protocol”: with 19/21 on 400 mg/kg over 5 days, 15/20 on 200 mg/kg, and 9/20 on placebo. The duration of response was longer in the 400 mg/kg group compared with placebo (log rank test  $P < 0.001$ ). There was an improvement in pemphigus activity score and antidesmoglein antibody titers. There was a dose–response trend, with superior results in the higher dosage group. Adverse events were similar in active and placebo arms.

### Are anti-inflammatory therapies (e.g., gold, dapsone, antibiotics) beneficial in pemphigus?

Anti-inflammatory agents are often prescribed for patients with relatively mild pemphigus, as they have a more favorable safety profile in comparison with immunosuppressants.

#### Gold

Auad and Auad described a blinded, placebo-controlled trial of adjuvant gold in 30 patients with pemphigus foliaceus [36]. The patients were initially stabilized on corticosteroids, and gold 3 mg/day or a placebo was then added. Nine of the 30 patients did not complete the trial, and an intention-to-treat analysis was not performed. The results for 10 patients treated with gold and 11 in the placebo arm were reported, with a mean follow-up of 4 years. At 12 months, a steroid-sparing effect was seen, with a mean steroid

dose of 37 mg in the placebo group and 5.5 mg/day in the gold arm. Four patients in the gold arm experienced complications, including diarrhea and proteinuria.

Four retrospective case series were indentified [37–40]. Most series have evaluated the use of gold in a population of patients with relatively mild disease. The majority of patients improved, a substantial proportion was able to stop treatment, and a small proportion failed to respond. A steroid-sparing effect was seen. Although side effects related to gold therapy were relatively mild, many patients were unable to tolerate treatment.

### Dapsone

Werth *et al.* reported an RCT that included 19 patients with pemphigus vulgaris who were unable to taper steroid below 15 mg/day after twice following a standardized prednisone-tapering schedule, plus any adjuvant, and were randomly assigned to dapsone 125–150 mg/day ( $n = 9$ ) or placebo ( $n = 10$ ), in addition to steroid and immunosuppressants [41]. Five of the nine patients receiving dapsone, in comparison with three of the 10 receiving the placebo, were able to taper steroids below 7.5 mg/day. There was a trend favoring dapsone, but statistical significance was not reached. Overall, side effects included a drug rash, paresthesias, and dyspnea secondary to methemoglobinemia.

Heaphy *et al.* reported the use of dapsone in a retrospective case series of nine patients with pemphigus vulgaris who where steroid dependent or had poorly controlled disease [42]. Dapsone was used as a third-line agent, in combination with steroids and immunosuppressive or anti-inflammatory adjuvants, at dosages of 125–150 mg/day. Seven of the nine patients were able to successfully taper steroids below 7.5 mg/day, and two patients were able to stop steroids. Two patients who had poorly controlled disease at baseline did not respond. The dapsone dose was adjusted in three of the nine patients in response to decreased hemoglobin.

Basset *et al.* reported a case series of nine previously untreated patients who received dapsone 200–300 mg/day [43]. Five patients, all with mild to moderate disease, responded with at least a 50% decrease in the extent of their disease within 15 days of starting therapy. Four patients did not respond. Three patients discontinued dapsone due to adverse events, including hemolytic anemia, toxic hepatitis, and methemoglobinemia.

### Tetracyclines

Antibiotics, including tetracycline and minocycline, have been used in pemphigus for their anti-inflammatory properties.

Calebotta *et al.* conducted a prospective case series with tetracycline [44]. Thirteen pemphigus vulgaris patients received tetracycline 2 g/day and prednisone 0.5–1.0 mg/kg per day. All patients treated with tetracycline and prednisone responded and achieved cessation of new blister formation within a mean of 5.4 days. Prednisone was able to be tapered within a mean of 17 days. Two of the 13 patients discontinued tetracycline due to adverse events, including sepsis and gastrointestinal upset.

In another case series by Alpsy *et al.*, 15 patients with pemphigus (11 with pemphigus vulgaris and four with pemphigus foliaceus) were treated with tetracycline 2 g/day and nicotinamide 1.5 g/day over 2 months [45]. Five patients were newly diagnosed and 10 had previously been treated with corticosteroids and/or immunosuppressive agents. All of the patients had active disease. At 2 months, two of the 15 patients had complete healing, four had 50% healing of lesions, and nine had no response. Three of the 15 patients had mild gastrointestinal upset. Chaffins *et al.* described 11 patients (six

with pemphigus vulgaris and five with pemphigus foliaceus) who were treated with tetracycline 2 mg/day and nicotinamide 1.5 mg/day [46]. Five of the 11 patients received concurrent prednisone (2.5–30 mg/day). At 2 months, five of the 11 patients had complete healing, four had 50% healing, and two had no response. Adverse events included gastrointestinal upset, headache, and a morbilliform eruption.

Gaspar *et al.* described 10 patients (seven with pemphigus vulgaris and three with pemphigus foliaceus) who were treated with minocycline 100 mg/day as an adjuvant [47]. Nine of the 10 patients were concurrently treated with prednisone (10–40 mg/day) and five patients also received azathioprine (100–200 mg/day). All of the patients had active disease when minocycline was commenced. Four of the 10 patients had complete clearing of lesions, two improved, and four had no response. A steroid-sparing effect was seen among responders. Minocycline was well tolerated; one patient developed pigmentation and nine developed candidiasis.

The evidence to support the use of antibiotics is inconsistent.

### Sulfasalazine and pentoxifylline

El-Darouti *et al.* reported a nonrandomized placebo controlled trial of adjuvant sulfasalazine and pentoxifylline involving 64 patients with pemphigus vulgaris [48]. Patients received concomitant pulsed steroid–cyclophosphamide therapy. Forty-two patients also received pentoxifylline 400 mg and sulfasalazine 500 mg t.d.s. A total of 86% of patients in the pentoxifylline/sulfasalazine group were classified as “excellent” clinical improvement, compared with 18% in the placebo arm. Serum tumor necrosis factor alpha titers were also decreased in the active group. Adverse events were predominantly gastrointestinal.

### Are biologicals effective and safe in pemphigus?

#### Rituximab

Rituximab has been evaluated in a number of case series. Joly *et al.* reported a prospective case series of 21 patients with corticosteroid-refractory or -dependent disease [49]. Patients were treated with a single cycle of four weekly infusions of rituximab 375 mg/m<sup>2</sup>. The number that achieved healing of all lesions by 3 months was 18/21, and the clinical response was sustained throughout the 34-month follow-up period by most patients. All patients demonstrated B-cell lymphopenia. Two patients experienced serious infections.

Horvath *et al.* reported a series of 15 patients treated with a single cycle of rituximab, involving two infusions of 500 mg 2 weeks apart [50]. Patients had varying disease severity and concomitant treatments. All patients demonstrated a clinical response, with mean time to disease control of 7 weeks, and sustained remission, with only 6/15 patients relapsing at a mean time of 97 weeks posttreatment. One patient experienced severe sepsis.

Arin *et al.* reported a case series of five patients refractory to prednisolone and azathioprine, treated with a single cycle of rituximab (375 mg/m<sup>2</sup> weekly for 4 weeks) [51]. Three out of five patients demonstrated a complete response and two out of five patients a partial response. Adjuvant immunosuppressants were able to be tapered in all patients. No serious adverse events were noted.

Lunardon *et al.* reported a retrospective series of 31 patients (24 pemphigus vulgaris, seven pemphigus foliaceus) treated with adjuvant rituximab [52]. Complete remission was achieved in 18/31 patients. Patients with shorter duration of disease before rituximab demonstrated superior response, raising the possibility that earlier treatment may decrease relapse; however, prospective studies are needed to evaluate this.



### Etanercept

Fiorrentino *et al.* reported a randomized placebo-controlled trial of etanercept for pemphigus vulgaris [53]. The trial was halted after a futility analysis after enrolment of eight patients. Treatment failed in five out of six patients in the etanercept group versus none out of two in the placebo group. Case reports have documented more positive results, possibly due to dosage considerations or heterogeneous response rates.

### Combinations therapy with rituximab and immunomodulatory therapy

Ahmed *et al.* reported a case series of 11 patients treated with refractory pemphigus vulgaris treated with rituximab and intravenous Ig [54]. The regimen involved a loading dose, then monthly infusions of both agents for 4 months. Nine of 11 patients responded, with a prolonged remission (mean 31 months). No infections were observed. The therapies were postulated to be synergistic.

Pfütze *et al.* reported a retrospective case series comparing six patients treated with immunoadsorption alone, and five patients treated with immunoadsorption and rituximab [55]. In this series, patients on combination therapy demonstrated superior clinical responses, decreased steroid dosages, and lower antibody levels.

### What is the role of adjuvant topical therapies?

Topical glucocorticoids are widely used; however, a range of novel topical therapies has been reported.

#### Clobetasol propionate

Dumas *et al.* reported a case series of seven patients with mild pemphigus vulgaris and pemphigus foliaceus who were treated with clobetasol propionate 0.05% cream alone, applied to affected sites on skin and mucosa twice daily [56]. Four of seven patients were controlled on topical therapy alone, while three patients required addition of systemic therapy.

#### Epidermal growth factor

There has been one left–right comparison RCT including 20 patients with pemphigus vulgaris with active lesions of symmetrical size and distribution [57]. All patients received concomitant systemic therapy with prednisolone with or without immunosuppressive agents. The intervention included epidermal growth factor (10 µg/g) in 0.1% silver sulfadiazine cream versus 0.1% silver sulfadiazine cream applied daily until complete healing was observed. The primary outcome measure was median healing time. Median healing time was 9 days versus 15 days (log rank  $P = 0.0003$ ). One patient developed disseminated zoster, but no other adverse effects were observed over a 9-month follow-up.

#### Nicotinamide gel

Iraji and Banan reported a left–right placebo-controlled trial of 4% nicotinamide gel involving 60 lesions of eight patients with pemphigus vulgaris [58]. Concomitant therapy included systemic corticosteroids and azathioprine. The percentage reduction in lesion surface area was greater in the nicotinamide group (26.2% vs –5.8%). One patient experienced temporary flushing.

#### Pimecrolimus

Iraji *et al.* reported a left–right placebo-controlled randomized trial of 1% pimecrolimus cream involving 62 lesions in 11 patients with pemphigus vulgaris [59]. Concomitant therapy included systemic corticosteroids and azathioprine. The percentage reduction in

lesion surface area was greater in the pimecrolimus group (15.7% vs –19.39%). Adverse effects included stinging at cream application site.

### Prostaglandin E2

Kumaran and Kanwar reported a case series of 10 patients with recalcitrant oral pemphigus vulgaris in whom systemic therapy had been discontinued [60]. The intervention included topical application of prostaglandin E2 b.i.d. to affected sites. Results were heterogeneous, with six patients improving and four patients failing therapy. Relapse upon cessation of therapy occurred within 7–10 days.

### Intralesional triamcinolone acetonide

Mignogna *et al.* reported a nonrandomized trial of adjuvant intralesional triamcinolone acetonide versus topical glucocorticoids in 35 patients with oropharyngeal pemphigus vulgaris [61]. Intralesional triamcinolone was administered at concentrations of 10 mg per lesion weekly for at least 2 weeks. The intralesional group experienced shorter time to remission (126.6 days vs 153.2 days), and lower cumulative steroid dosages (4894 mg vs 5312 mg); however, the difference was not statistically significant. Patient satisfaction and pain scores were superior in the intralesional group. Candidiasis was less common in the intralesional group (6% vs 37%).

### What therapies are available to minimize side effects of treatment?

#### Bisphosphonates

Tee *et al.* reported an RCT of 44 patients with newly diagnosed immunobullous disorders (11 pemphigus vulgaris, 11 pemphigus foliaceus) comparing oral alendronate sodium 10 mg/day versus placebo [62]. Intention-to-treat analysis was not performed. All patients received concomitant vitamin D and calcium. All patients were treated with oral prednisolone, with some patients also receiving adjuvant azathioprine or dapsone. There was a significant difference in bone mineral density (+3.5% alendronate, –1.4% placebo lumbar spine  $T$  score;  $P = 0.01$ ). No new fractures were identified in either group.

#### Key points

- Pemphigus is a rare disease, and consequently the majority of trials conducted to date have been limited by inadequate power.
- Low-dose (1 mg/kg) corticosteroids appear to be as equally effective as higher dose regimens for initial disease control.
- Pulsed corticosteroid therapy confers no additional benefit in newly diagnosed patients and is associated with increased morbidity.
- Adjunctive immunosuppressants (azathioprine, cyclophosphamide, mycophenolate mofetil) have a steroid-sparing benefit. The optimal steroid-sparing agent is not established. Cyclosporine does not appear beneficial.
- Plasmapheresis is not indicated in new-onset disease. Intravenous Ig and immunoadsorption appear to be beneficial.
- Dapsone and gold may have a steroid-sparing effect.
- Rituximab appears to prolong duration of remission, although infection rates may be increased. Etanercept does not appear to be beneficial.
- A variety of novel topical therapies may reduce healing time.
- Adjuvant bisphosphonates improve bone mineral density.
- Choice of treatment requires consideration of disease severity, co-morbidities, and evaluation of risks and benefits of therapies on an individual basis.



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# Cutaneous sarcoidosis

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## Background

### Definition

Sarcoidosis is a systemic, idiopathic disease characterized by the formation of noncaseating epithelioid granulomas that disrupt underlying tissue function. While sarcoidosis can affect virtually any organ system, pulmonary (>90%), hepatosplenic (50–80%), hematological (40%), musculoskeletal (39%), ocular (30–50%), cutaneous (25%), cardiac (5%), and neurological (5–10%) manifestations are most common [1,2].

Cutaneous manifestations of sarcoidosis typically present at disease onset, and – with the exception of erythema nodosum and lupus pernio – do not correlate with disease severity. Erythema nodosum tends to be associated with acute, benign, spontaneously resolving sarcoidosis, whereas the presence of lupus pernio may suggest a more treatment-refractory course [3–5]. Skin lesions in sarcoidosis can be divided into specific lesions (i.e., skin biopsy demonstrates noncaseating granulomas) and nonspecific lesions (i.e., reactive states). Specific lesions include papules, nodules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio. Multiple atypical presentations also exist (i.e., verrucous, ulcerative, and morpheaform). Plaques and papules are the most common cutaneous lesions, while lupus pernio is most specific for sarcoidosis [6]. Lupus pernio tends to affect the face, manifesting as brownish-red, dusky, swollen, and shiny infiltrated plaques [1].

### Incidence/prevalence

Sarcoidosis affects all ethnic groups, ages, and both sexes, but incidence peaks in adults under 40 years of age [7]. Sarcoidosis is most common in African-American females, whose disease is typically more acute and severe in comparison with others [8,9]. In the USA, the incidence is 10–14 per 100 000 for whites and 35.5–64 per 100 000 for African-Americans [10].

### Etiology

The etiology of sarcoidosis remains elusive, with immunologic, infectious, genetic, and environmental factors all postulated to play a role. The genetic basis for sarcoidosis has been demonstrated in

some family clusters of disease, including a fivefold increased risk of sarcoidosis in siblings and relatives of infected individuals, while spouses of sarcoidosis patients lack an increased risk [11]. Serological studies have found increased susceptibility in patients with certain class I and II human leukocyte antigen serotypes, and mutations within other immune genes, including tumor necrosis factor (TNF) gene mutations, have been seen in some populations [11–15]. Clustering of cases, and the occurrence of sarcoidosis-like granulomatous pulmonary disease in cases of beryllium exposure and first-responders in the September 11, 2001, attacks, have led investigators to search for environmental factors [12]. Occupational exposures to insecticides and pesticides carry a slightly increased risk of disease development, but some have speculated that this may be due to a microbe-rich environment [16]. While numerous pathogens have been examined, a potential causative role for mycobacteria has been the primary focus, because of the granulomatous nature of this disease, but no definitive proof (no mycobacterium cultured from sarcoidosis lesions) has emerged thus far [1]. As diagnostic techniques have become more sophisticated, evidence of either mycobacterial DNA or proteins have been found in increasing numbers of sarcoidosis samples studied [12].

### Prognosis

Sarcoidosis has a variable course, with both limited/spontaneously resolving and chronic/progressive forms of disease. Most patients with sarcoidosis do well. The disease resolves spontaneously in up to 60% of patients, and only about 5% of sarcoidosis patients will eventually die of their disease [17,18]. In the USA, patients are most likely to die of pulmonary complications such as pneumonia, pulmonary fibrosis progressing to cor pulmonale, and chronic obstructive pulmonary disease; deaths may occur due to cardiac or neurosarcoidosis as well [19].

### Diagnostic tests

Because no specific diagnostic test exists, sarcoidosis remains a diagnosis of exclusion. Diagnostic evaluation of a patient with suspected sarcoidosis may include [1,18]:

- *Detailed history and physical examination:* with emphasis on lungs, skin, eyes, nervous system, and heart.

- **Chest radiography.** The stages are not chronological:
  - Stage 1 – bilateral hilar, with or without paratracheal adenopathy;
  - Stage 2 – adenopathy with pulmonary infiltrate;
  - Stage 3 – pulmonary infiltrates only;
  - Stage 4 – pulmonary fibrosis.
- **Pulmonary function tests:** restrictive pattern with decreased diffusing capacity ( $DL_{CO}$ ).
- **Biopsy of affected tissue:** noncaseating granulomas.
- **Serum chemistries:** elevated alkaline phosphatase and/or hypercalcemia, which are not specific for sarcoidosis.
- **Angiotensin-converting enzyme levels:** generally, not a useful guide for diagnosis or monitoring of therapeutic response.
- **Electrocardiography:** cardiac sarcoidosis may be minimally symptomatic, and all patients should undergo baseline screening; additional imaging, including echocardiography, cardiac magnetic resonance, or positron emission tomography, may be necessary in select patients.
- **Expanded organ-specific testing guided by history and symptoms:** patients with neurologic symptoms may warrant further targeted imaging. Patients with a history of kidney stones may warrant detailed urine studies. Patients with abnormal calcium levels may warrant vitamin D testing. Patients with positive review of symptoms may warrant thyroid investigation. Patients with joint pains may benefit from imaging and rheumatologic consultation.

## Aims of treatment

Disfiguring skin lesions represent an indication for treatment of cutaneous sarcoidosis. Multiple available treatment modalities include topical and intralesional steroids, oral steroids, antimalarials, various immunosuppressive agents, and other medical and physical interventions. Since cutaneous sarcoidosis may spontaneously regress, and since many available therapeutic modalities carry a risk for substantial toxicity, it is important to weigh the risks and benefits carefully. Nonetheless, patients often seek treatment because of poor cosmesis produced by cutaneous sarcoidosis, especially when disease leads to disfiguring or nondisfiguring lesions on the head and neck. Additionally, in some patients, the cutaneous manifestations may improve with treatment of systemic disease, but in others the skin involvement is discordant and requires targeted skin-specific therapy. Accordingly, dermatologists should become familiarized with the evidence-based treatment options available for cutaneous sarcoidosis.

## Relevant outcomes

Outcome measures in cutaneous sarcoidosis are limited to subjective evaluation of whether therapy decreases or resolves active skin lesions. No validated scoring method is widely used for this disease, though one has recently been introduced [20]. Studies reporting response range from physician impression, to lesion counting, to comparison of before-and-after photography. The definition of disfiguring lesions is not well established among different investigators, and there is a lack of uniformity in measuring clinical end points in response to therapy due to polymorphic cutaneous manifestations.

## Methods of search

We searched the Cochrane Library for “sarcoidosis or sarcoid.” We searched MedlinePubMed from 1966 to 2012 using the terms “cutaneous sarcoidosis,” or “sarcoidosis,” or “lupus pernio” and “therapeutics,” or “treatment,” or “prednisone,” or “steroids,” or

“glucocorticoids,” or “allopurinol,” or “chloroquine,” or “hydroxychloroquine,” or “antimalarial,” or “methotrexate,” or “thalidomide,” or “leflunomide,” or “mycophenolate mofetil,” or “azathioprine,” or “pentoxifylline,” or “apremilast,” or “tretinoin,” or “isotretinoin,” or “tetracyclines,” or “minocycline” or “allopurinol,” or “tacrolimus,” or “infliximab,” or “adalimumab,” or “etanercept,” or “alefacept,” or “tranilast,” or “chlorambucil,” or “colchicine,” or “cyclosporine,” or “ultraviolet,” or “photodynamic therapy,” or “surgery,” or “intralesional,” or “pulse dye laser,” or “laser” as subject headings or titles or key words.

## Questions

### Case scenario 66.1

The patient is a 44-year-old African-American woman with a 14-year history of sarcoidosis. The patient has asymptomatic pulmonary involvement that does not require treatment. However, she is requesting treatment for noticeable facial lesions (Figure 66.1).

### What are the effects of systemic therapeutic interventions in patients with cutaneous sarcoidosis?

#### Oral steroids

##### Benefits

Oral glucocorticoids are used in systemic sarcoidosis because of their anti-inflammatory and immunosuppressive actions, and are often offered as first-line treatment for cutaneous sarcoidosis [21,22] despite scant, and largely anecdotal, evidence to support their use for this indication [23–33].

Mosam and Morar treated 30 patients with cutaneous sarcoidosis, of which, none of 30 responded to systemic steroids alone. These patients required a sequential therapeutic ladder (chloroquine, methotrexate, doxycycline, allopurinol, isotretinoin, azathioprine, thalidomide) to help achieve a positive clinical outcome [34]. Ramos-Casals *et al.* reviewed the literature on patients with cutaneous sarcoidosis triggered by antiviral therapy for hepatitis C virus infection. They noted nine patients treated with glucocorticoids had improvement in skin lesions and 11 with skin involvement had improvement with the discontinuation with antiviral therapy alone [35]. Jung and Roh noted therapy with oral glucocorticoids alone allowed partial responses in seven of eight patients with specific lesions of cutaneous sarcoidosis [36].



Figure 66.1 Cutaneous sarcoidosis.



### Harms

The multiple complications of steroid therapy are well known, and their likelihood and severity correlate with the length of administration. Complications may include glucose intolerance, increased susceptibility to infection, osteoporosis, avascular bone necrosis, cataracts, and neuropsychiatric changes [37]. A study of 441 sarcoidosis patients with a mean of two organ systems involved treated with prednisone who were followed for a mean of 2.9 years revealed that greater use of systemic corticosteroids was associated with a small but significant rise in health-care utilization related to infections and emergencies not directly attributable to sarcoidosis [38].

### Comments/implications for clinical practice

There are no randomized controlled trials (RCTs) or systematic reviews to support the use of oral steroids for cutaneous sarcoidosis. In the articles reviewed above, 17 of 56 patients treated with oral steroids as monotherapy had positive results. This is insufficient evidence to conclude that oral steroids are effective in cutaneous sarcoidosis. Hence, large RCTs are needed to establish clear benefit. Despite the lack of definitive studies showing the effectiveness of oral steroids in cutaneous sarcoidosis, many dermatologists still use them as first-line therapy, since steroids reverse the manifestations of pulmonary and other extrapulmonary manifestations of disease [7,37].

### Antimalarials

Antimalarials, such as chloroquine and hydroxychloroquine, are 4-aminoquinolones, and represent an effective therapy for connective-tissue diseases. Their immunomodulatory properties form the rationale for their use in cutaneous sarcoidosis.

### Benefits

While there are no RCTs to support the effectiveness of antimalarials in cutaneous sarcoidosis, their benefit has been reported in a number of open, nonrandomized, noncontrolled, prospective studies. In a 1991 comprehensive literature review of antimalarials in cutaneous sarcoidosis, Zic *et al.* concluded that chloroquine should be strongly considered in patients for whom the main indication for treatment is disfiguring cutaneous lesions, while corticosteroids should remain first-line treatment for patients with extracutaneous sarcoidosis [39]. The authors recommended an initial 14-day course of chloroquine, 500 mg/day, followed by long-term therapy with 250 mg/day, on the basis of published data [40–45]. In addition, Ben Jennet *et al.* noted in a review of 28 cases of cutaneous sarcoidosis that seven of 13 patients treated with chloroquine ameliorated their disease [46]. Modi and Rosen reported three cases of micropapular cutaneous sarcoidosis responsive to hydroxychloroquine at 200 mg twice daily [47].

Meyersburg *et al.* in 2011 reported a single case of ulcerative cutaneous sarcoidosis of the leg responding to hydroxychloroquine and compression therapy [48].

### Harms

Long-term administration of either chloroquine or hydroxychloroquine may lead to various ocular complications, the most serious of which are irreversible retinopathy and blindness [39]. Hydroxychloroquine has a lower risk of ocular toxicity, but also less effectiveness in sarcoidosis [18,39]. Thus, periodic ophthalmological examinations should be carried out in any patient on long-term therapy [49,50]. Other common side effects include nausea and vomiting, gastrointestinal upset, central nervous system toxicity

(irritability, nervousness, depression), neuromuscular reactions (skeletal muscle palsies, myopathy, or neuromyopathy), and cutaneous pigmentation. Millard *et al.* reported drug-induced bullous pemphigoid in a male patient treated with 3 months of chloroquine for sarcoidosis [51].

### Comments/implications for clinical practice

The articles summarized above describe experience with a total of 120 patients treated with antimalarials, 93 of whom had a positive result. While none of these articles represents a large RCT, these studies as a whole suggest that chloroquine and hydroxychloroquine represent a reasonable treatment option for patients with cutaneous sarcoidosis.

### Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor widely used in the treatment of neoplastic diseases owing to its antiproliferative actions, and in chronic inflammatory conditions as a nonsteroidal immunosuppressant.

### Benefits

There are no RCTs or systematic reviews of methotrexate in cutaneous sarcoidosis [52,53], and the evidence for its effectiveness is based on open, nonrandomized, noncontrolled studies. In the first study of methotrexate for cutaneous sarcoidosis, Veien and Brodthagen reported clearance of skin lesions in 12 of 16 patients treated with 25 mg/week. Two patients discontinued treatment because of nausea [53]. Lower and Baughman reported improvement of cutaneous disease in 16 of 17 patients treated with methotrexate as a steroid-sparing agent for over 2 years (the average dose in the 55 study patients was 28 mg/day) [54]. Kaye *et al.* reported complete regression of severe recalcitrant cutaneous sarcoidosis in one patient, and significant improvement in three patients, treated with methotrexate, 10 mg/week, for 30 months [55]. Gedalia *et al.* reported resolution of cutaneous sarcoidosis in two of three pediatric patients treated with 10–15 mg/week of methotrexate, with significant reduction of oral steroid doses while on methotrexate [56]. Lacher reported improvement of steroid-resistant cutaneous sarcoidosis in one patient after the initial combination of prednisone 75 mg three times weekly and methotrexate 40 mg twice weekly, followed by methotrexate 7.5 mg twice weekly and eventual tapering of the steroid [57]. Webster *et al.* reported improvement of severe steroid-resistant cutaneous sarcoidosis in three patients after methotrexate 15.0–22.5 mg/week [58]. Henderson *et al.* reported improvement of cutaneous sarcoidosis in a male patient with steroid-resistant laryngeal and cutaneous disease after 10 mg/week of methotrexate [59]. Gary *et al.* reported complete remission of recalcitrant cutaneous sarcoidosis in three of four patients after treatment with methotrexate at dosages ranging from 12.5 mg/week to 30 mg/week after a mean treatment duration of 29 months. Side effects of methotrexate were observed in one patient (elevated liver enzymes), leading to discontinuation of methotrexate [60].

### Harms

Complications of methotrexate therapy include bone-marrow suppression, nausea and vomiting, hepatotoxicity, and hypersensitivity pneumonitis [37]. Albertini *et al.* described a patient with severe systemic and ulcerative sarcoidosis who was started on methotrexate 25 mg/week [61]. Although her ulcerative lesions initially regressed, she soon developed anemia, leukopenia, and an elevated aspartate transaminase level, necessitating the withdrawal of

methotrexate. The patient subsequently died of her disease. Major toxic effects noted by Lower and Baughman were hepatotoxicity, leukopenia, and cough [54]. However, a patient with cutaneous and bone-marrow sarcoidosis had improvement of anemia and leukopenia with combination methotrexate and mycophenolate mofetil [62].

#### **Comments/implications for clinical practice**

The articles published to date describe experience with a total of 50 patients with cutaneous sarcoidosis treated with methotrexate, of whom 42 had positive results. While none of these articles represents a large RCT, and there is little consistency across the trials with regard to the patient population, dosage, or clinical end points, the aggregate evidence from these studies suggests that methotrexate might be useful as a steroid-sparing agent in patients who require an additional or alternative therapeutic option.

#### **Mycophenolate mofetil**

Mycophenolate mofetil acts via inhibition of purine synthesis, blocking proliferation of T- and B- lymphocytes. It is approved for renal allograft rejection prevention and heart transplant immunosuppression, and used in a variety of inflammatory disorders.

#### **Benefits**

Kouba *et al.* reported one series of five patients with sarcoidosis involving the skin, all of whom showed improvement on doses ranging from 30 to 45 mg/kg per day, with improvement noted on average at 3 months of therapy [63]. Notably, these patients were also receiving hydroxychloroquine and systemic corticosteroids, but were able to dose-reduce their systemic steroids while on mycophenolate therapy.

#### **Harms**

Generally, mycophenolate is well tolerated, with some patients noting gastrointestinal discomfort that may be dose dependent; the study above noted no adverse effects. As an immunosuppressive medication, mycophenolate mofetil can increase the incidence of infections, including zoster.

#### **Comments/implications for clinical practice**

There is a lack of high-quality data; the one study published regarding mycophenolate for cutaneous sarcoidosis noted improvement and successful systemic corticosteroid dose reduction with no adverse events in a small series of patients. This is insufficient evidence to conclude that mycophenolate is beneficial for the treatment of cutaneous sarcoidosis. RCTs will therefore be necessary to evaluate fully the efficacy and long-term safety in patients with cutaneous sarcoidosis.

#### **Leflunomide**

Leflunomide is an anti-inflammatory cytotoxic drug that inhibits pyrimidine synthesis. It is used in the management of patients with rheumatoid arthritis. The drug exerts its effects via a reversible selectivity for proliferating lymphocytes [64]. Anti-inflammatory properties form the basis of its use in cutaneous sarcoidosis.

#### **Benefits**

Majithia *et al.* reported 20 mg/day of leflunomide allowing marked improvement in the skin rash of sarcoidosis in a patient that failed methotrexate, hydroxychloroquine, and prednisone [65]. Baughman and Lower in 2004 studied the use of leflunomide in 32 patients

with sarcoidosis who had multiorgan involvement, including skin, and noted 12 of 17 who completed treatment had a complete or partial response, though cutaneous response was not specifically commented on [66].

#### **Harms**

The advantage of leflunomide has been its toxicity profile is less than that of other immunosuppressants. However, patients may experience gastrointestinal side effects and infrequently cutaneous significant drug reactions [64–66].

#### **Comments/implications for clinical practice**

The articles published to date describe only one case of cutaneous disease responding, though Baughman and Lower's results are not specifically commented on. Patients had only mild or moderate side effects. This is insufficient evidence to conclude that leflunomide is beneficial for the treatment of cutaneous sarcoidosis, particularly because cutaneous sarcoidosis often resolves spontaneously. RCTs will therefore be necessary to evaluate fully the efficacy and long-term safety of leflunomide in patients with cutaneous sarcoidosis.

#### **Thalidomide**

Thalidomide was originally marketed as a sedative, but was withdrawn in 1962 because of its teratogenic effects [67]. Thalidomide at low doses is effective in the treatment of erythema nodosum leprosum and lupus erythematosus [68]. Thalidomide inhibits TNF- $\alpha$ , interferon gamma and interleukin (IL)-12, and increases IL-2. TNF- $\alpha$  and interferon gamma are the major cytokines that drive granulomatous inflammation in sarcoidosis, while IL-2 counteracts the effects of interferon gamma and TNF- $\alpha$  [69]. Based on its mechanism of action, thalidomide may be effective in the treatment of cutaneous sarcoidosis.

#### **Benefits**

There are no RCTs or systematic reviews of thalidomide in cutaneous sarcoidosis. Estines *et al.* reported complete regression of severe and disfiguring recalcitrant cutaneous sarcoidosis in three patients and incomplete regression in four among 10 patients treated with thalidomide 1.84 mg/kg. The dose was gradually reduced for five of the seven responders; three of the five relapsed, but improved after restarting at the same dose [70]. Baughman *et al.* reported an open-label, dose-escalation trial of thalidomide in 14 patients with lupus pernio unresponsive to prior therapy who completed 4 months of thalidomide. All patients experienced some subjective improvement of skin lesions, and 10 of 12 evaluable patients showed objective improvement using photograph scoring. Five patients improved after 1 month (treated with 50 mg/day of thalidomide), seven more patients improved after 2 months (treated with 100 mg/day of thalidomide in the second month), and two patients required an additional month of 200 mg/day of thalidomide to achieve a response [71].

A retrospective evaluation of thalidomide 100–200 mg/day in 12 patients with cutaneous sarcoidosis, by Nguyen *et al.*, found that lesions regressed in 10 of 12 treated patients within 1–5 months of therapy, with an average time of 2–3 months. Four of the patients achieved complete responses, six had partial responses, and two showed no response [72]. In an open study by Oliver *et al.*, five of eight patients with chronic cutaneous sarcoidosis had flattening of skin lesions, while one developed enlarging and ulcerating skin lesions, after 16 weeks of thalidomide. Treatment was started at an initial dosage of 50 mg/day, and doubled monthly to a maximum

dosage of 200 mg/day. All lesions became hyperpigmented during the study period, which the authors characterized as an improvement, and all follow-up biopsies showed decreased granuloma size and decreased epidermal thickness. After discontinuing thalidomide, all of the treated patients relapsed [73].

Carlesimo *et al.* reported clinical improvement of steroid-resistant cutaneous sarcoidosis in a 56-year-old woman after 2 weeks of thalidomide 200 mg/day, followed by 100 mg/day for 11 weeks [67]. Rousseau *et al.* reported clinical improvement of recalcitrant cutaneous sarcoidosis in a 30-year-old woman after thalidomide 100 mg/day for 2 months, gradually tapered to a maintenance dose of 50 mg/day [68]. Lee and Koblenzer reported clinical improvement of cutaneous sarcoidosis in a 59-year-old patient after thalidomide 200 mg/day for 2 months and 300 mg/day for 4 months [74]. Hoch *et al.* reported almost complete resolution of generalized or disseminated cutaneous sarcoidosis in two patients after 8–12 months of treatment with thalidomide, initially with 200 mg/day and later with 100 mg/day [75]. Walter *et al.* reported rapid improvement of therapy-resistant long-standing cutaneous sarcoidosis in a 36-year-old man after thalidomide 50 mg/day, without major adverse effects [76]. Fazzi *et al.* treated 19 sarcoidosis patient with cutaneous and pulmonary disease for 24 months (200 mg/day for 2 weeks, then 100 mg/day for 11 weeks, followed by 100 mg every other day for 35 weeks, then tapered). Significantly ( $P < 0.05$ ) lower skin scores occurred at 3- (6/19) and 6-month (12/18) evaluations. However, 42% of the patients discontinued therapy due to developing symptoms of neuropathy [77]. Notably, Doherty and Hsu noted no response to thalidomide in two patients with cutaneous sarcoidosis [78].

### Harms

Thalidomide therapy may be complicated by neurosensory, gastrointestinal, and teratogenic effects [67,74]. In their analysis of thalidomide for cutaneous sarcoidosis, Baughman and Lower reported that the most serious adverse effect is peripheral neuropathy, which often resolves by reducing the dose or discontinuing the medication [79]. Baughman *et al.* noted neuropathy in seven of 14 patients, somnolence in nine patients, dizziness in two patients, constipation in six patients, rash in one patient, and increasing shortness of breath in one patient [71]. Nguyen *et al.* also noted nasopharyngeal, pulmonary, hepatic, and neurologic side effects in their retrospective analysis, and reported one patient who developed deep vein thrombosis while on thalidomide [72].

### Comments/implications for clinical practice

The articles published to date describe experience with 69 patients treated with thalidomide, 50 of whom had positive results. While none of these articles represents a large RCT, and there is inconsistency across the trials with regard to patient population, dosage, and clinical end points, the aggregate evidence from these studies suggests that thalidomide may represent a reasonable alternative or additional therapeutic option in cutaneous sarcoidosis. A large RCT will thus be necessary in order to obtain definitive proof.

### Tetracyclines

Tetracyclines are antibiotics that inhibit T-cell proliferation and granuloma formation in vitro [80], which forms the rationale for their use in cutaneous sarcoidosis.

### Benefits

There are no RCTs or systematic reviews of tetracyclines in cutaneous sarcoidosis. In one nonrandomized, noncontrolled, open pro-

spective study, eight of 12 patients with recalcitrant cutaneous sarcoidosis had complete regression, two had partial regression, and two had treatment failure (one progressed and one remained stable) after 12 months of minocycline 200 mg/day. After withdrawal of therapy, three of the 10 responders relapsed [80]. Antonovich and Callen reported complete clearance of lesions in a patient with cutaneous sarcoidosis induced by cosmetic tattoo after a 4-month course of doxycycline 100 mg twice a day combined with a mid-potency topical steroid [81]. Additional case reports reported similar resolution of cutaneous sarcoidosis both with minocycline and doxycycline therapy [82,83].

### Harms

General side effects of tetracyclines include photosensitivity, gastrointestinal symptoms, and pseudotumor cerebri. Side effects of minocycline include nausea and vomiting, hypersensitivity reactions, blue skin pigmentation, and vertigo [80]. Hypersensitivity was noted in one patient in this study [80].

### Comments/implications for clinical practice

The articles published to date describe experience with a total of 15 patients treated with tetracyclines, 13 of whom had positive results. While this is insufficient evidence to conclude that tetracyclines are beneficial for the treatment of cutaneous sarcoidosis and a large RCT will be necessary for definitive proof, tetracyclines may represent an easy alternative to oral steroids or other medications with a more serious side-effect profile.

### Allopurinol

Allopurinol is a xanthine oxidase inhibitor used in the treatment of gout and other inflammatory diseases. Its anti-inflammatory properties form the basis for its use in cutaneous sarcoidosis.

### Benefits

There are no RCTs or systematic reviews of allopurinol in cutaneous sarcoidosis. In one nonrandomized, uncontrolled, open prospective study, four of six patients with cutaneous sarcoidosis had improvement of skin lesions after treatment with allopurinol, starting at 100 mg/day and increased to 600 mg/day by 100 mg every 2–4 weeks [84]. Bregnhøj and Jemec reported a positive response in four of seven patients with cutaneous sarcoidosis who were treated with low-dose allopurinol [85]. Pfau *et al.* reported complete resolution of scar sarcoidosis in two patients and partial resolution of nodular sarcoidosis in two patients after treatment with allopurinol 300 mg/day over a 3–7-month period [86]. Rosof reported remission of cutaneous sarcoidosis in two patients treated with allopurinol [87]. Pollock reported marked improvement of cutaneous sarcoidosis lesions in two patients after treatment with allopurinol, either 100 mg/day or 300 mg/day [88]. Brechtel *et al.* reported improvement of recalcitrant disseminated cutaneous sarcoidosis in one patient after allopurinol 300 mg/day [89]. Antony and Layton reported improvement of recalcitrant cutaneous acral sarcoidosis after allopurinol 300 mg/day [90]. El-Euch *et al.* reported improvement in one child after allopurinol 200 mg/day [91]. Notably, Voelter-Mahlknecht *et al.* reported one patient whose cutaneous sarcoidosis progressed while on allopurinol [92].

### Harms

Allopurinol therapy may be complicated by a drug rash (including a severe reaction, such as toxic epidermal necrolysis), as well as nausea and vomiting, hepatotoxicity, and bone-marrow suppression [89].

### Comments/implications for clinical practice

The articles published to date describe experience with a total of 26 patients treated with allopurinol, 20 of whom had a positive result. This is insufficient evidence to conclude that allopurinol is beneficial for treatment of cutaneous sarcoidosis, particularly because cutaneous sarcoidosis often resolves spontaneously. Large RCTs will be necessary for definitive proof.

### Isotretinoin

Isotretinoin, a retinoid that inhibits sebaceous gland function and keratinization, is useful in the treatment of many dermatological conditions. The immunomodulatory effects of isotretinoin form the basis for its use in cutaneous sarcoidosis [93].

### Benefits

There are no RCTs or systematic reviews of isotretinoin in cutaneous sarcoidosis. Georgiou *et al.* described complete resolution of recalcitrant, long-standing cutaneous sarcoidosis in a 31-year-old woman after 8 months of isotretinoin 1 mg/kg per day [93]. Waldinger *et al.* reported resolution or improvement of many long-standing severe disfiguring and recalcitrant lesions in a woman after 30 weeks of isotretinoin (initially 40 mg/day for 6 weeks, increased to 80 mg/day for 16 weeks, and decreased back to 40 mg/day for the last 8 weeks because of side effects) [94]. Spiteri and Taylor reported negligible resolution of chronic cutaneous sarcoid nodules in a woman treated with isotretinoin, 75 mg/day (decreased to 50 mg/day because of cheilitis), whose exfoliative dermatitis prompted drug withdrawal after 7 weeks [95]. Vaillant *et al.* reported improvement of recalcitrant cutaneous sarcoidosis in a woman after 6 months of isotretinoin 0.4–1.0 mg/kg per day [96]. Mosam and Morar reported clearance of multitherapy-resistant cutaneous sarcoidosis in one patient after 6 months of isotretinoin therapy at 25 mg/day [34]. Chong *et al.* reported on a series of patients, one of whom was a Chinese patient with acne and sarcoidosis who obtained a partial response to isotretinoin [97].

### Harms

Isotretinoin is a teratogenic drug and must not be used by women who are pregnant or who become pregnant during treatment. Other side effects include visual impairment, hepatic dysfunction, and pancreatitis. Side effects noted by study participants included myalgia, xerosis, dryness of nasal mucosa, cheilitis, and exfoliative dermatitis [93,94,96].

### Comments/implications for clinical practice

The articles published to date describe experience with six patients treated with isotretinoin, five of whom had a positive result. This is insufficient evidence to conclude that isotretinoin is beneficial for the treatment of cutaneous sarcoidosis, particularly because cutaneous sarcoidosis often resolves spontaneously. Large RCTs will be necessary for definitive proof.

### Fumaric acid esters

Fumaric acid esters (FAEs) represent a form of immunomodulatory therapy that has been used successfully in Europe for the treatment of psoriasis. FAEs inhibit the pathogenetic mechanisms of granuloma formation, namely the downstream effects of TNF- $\alpha$ , maintenance of a Th1 environment, and proliferation of lymphocytes [98,99]. FAEs may therefore have efficacy in treatment of cutaneous sarcoidosis.

### Benefits

There are no RCTs or systematic reviews of FAEs in cutaneous sarcoidosis. Breuer *et al.* treated 11 patients with recalcitrant cutaneous sarcoidosis with FAE. Three of the patients treated with five or six tablets per day for 12–23 months had significant improvement of disease, while three of the patients treated with four to six tablets for 4–7 months had slight to moderate improvement of disease. Treatment was discontinued in five of the patients due to a lack of effect, and four of the patients had side effects that prompted discontinuation of therapy, including leukopenia, nausea, proteinuria, and flushing [99]. Gutzmer *et al.* reported a 61-year-old woman with cutaneous sarcoidosis whose lesions markedly improved after 12 months of therapy with FAEs. A recurrence of cutaneous disease 18 months after discontinuation was treated successfully with a 2-month course of FAEs [100]. Nowack *et al.* reported on three women with recalcitrant cutaneous sarcoidosis whose disease completely cleared after 4–12-month courses of FAEs dosed in accordance with the standard therapy regimen for psoriasis. Side effects included flushing, minor gastrointestinal complaints, and lymphopenia [101]. In addition, Dummmler *et al.* described two patients with cutaneous sarcoidosis, one of whom who had a significant improvement after 4 months of treatment with FAE; the second patient showed a slight therapeutic response after 2 months of therapy [102]. Wolter *et al.* reported an individual with resolution of cutaneous and pulmonary sarcoidosis over an 11-month course of FAE therapy [103], while Klein *et al.* reported a partial clearance in the skin lesions of one sarcoidosis patient treated with fumarate therapy [104].

### Harms

FAEs have been associated with several types of side effects in most treated patients with granulomatous skin diseases. The most frequent side effects of FAEs are flushing and diarrhea. Others include abdominal discomfort, nausea, flatulence, lack of appetite, and fatigue [34]. FAEs may produce leukopenia, relative lymphopenia, eosinophilia, and elevation of liver function tests, all of which resolve spontaneously after dose reduction or discontinuation of the treatment [98]. Hoefnagel *et al.* have evaluated the long-term safety of FAEs in 66 patients with severe psoriasis, 41 of whom received FAEs for at least 1 year and 12 of whom had received FAEs for 10–14 years. Seventy-three percent of the patients reported adverse events, which were usually mild and mainly consisted of flushing (55%), diarrhea (42%), nausea (14%), fatigue (14%), and abdominal complaints (12%). Seventy-six percent of the patients had relative lymphocytopenia during therapy with FAEs, and 14% and 25% of the patients had transient eosinophilia and moderate liver enzyme elevations, respectively. The authors concluded that FAEs are a safe long-term treatment in patients with severe psoriasis [105].

### Comments/implications for clinical practice

The articles published to date describe positive results in 14 of 19 patients in whom FAE therapy led to improvement or resolution of disease. Patients had only mild or moderate side effects. This is insufficient evidence to conclude that FAEs are beneficial for the treatment of cutaneous sarcoidosis, particularly because cutaneous sarcoidosis often resolves spontaneously. RCTs will therefore be necessary to evaluate fully the efficacy and long-term safety of FAEs in patients with cutaneous sarcoidosis.

### Phosphodiesterase inhibitors

Pentoxifylline is a nonspecific inhibitor with anti-inflammatory properties demonstrated by its ability to inhibit IL-2, IL-2 receptor



expression, and TNF production. Park *et al.* reported its steroid-sparing effects in the treatment of pulmonary sarcoidosis in an RCT [106]. However, no skin disease was evaluated in this article, and review of the literature reveals no data of its use for cutaneous sarcoidosis. A new-generation phosphodiesterase type 4 inhibitor, Apremilast, which has similar anti-inflammatory properties, has been used in treatment of cutaneous sarcoidosis [107].

### Benefits

Owing to apremilast's tendency to cause less gastrointestinal disturbance compared with pentoxifylline, it has been used in an open noncontrolled trial of 15 patients with chronic cutaneous sarcoidosis that had been unresponsive to systemic therapy for 3 months prior to entry to the study [107]. Apremilast was given at 20 mg twice a day. A total of 46 skin lesions were evaluated for induration, erythema, desquamation, and area of involvement. A significant reduction in induration score only was noted ( $P < 0.05$ ) at 12 weeks. Currently, apremilast is not available in the USA.

### Harms

Apremilast appeared well tolerated in the Baughman *et al.* study [107]. Only two of 15 patients required a dose reduction to 20 mg once daily because of jitteriness and nausea.

### Comments/implications for clinical practice

The articles published to date describe positive results in 15 patients that had a total of 46 indurated skin lesions of sarcoidosis. Patients had only mild or moderate side effects. This is insufficient evidence to conclude that apremilast is beneficial for the treatment of cutaneous sarcoidosis, particularly because cutaneous sarcoidosis often resolves spontaneously. RTCs will therefore be necessary to evaluate fully the efficacy and long-term safety of FAEs in patients with cutaneous sarcoidosis.

### Biologic anti-TNF- $\alpha$ agents

Monoclonal anti-TNF- $\alpha$  antibodies (infliximab, adalimumab) as well as the soluble anti-TNF- $\alpha$  receptor (etanercept) neutralize soluble and cell-bound TNF- $\alpha$ , and have been widely used in the treatment of psoriasis and inflammatory bowel disease in the past 15 years. The antibodies appear to have increased potency in comparison with the soluble receptor due to their cytolytic effects against immune cells with membrane-resident TNF- $\alpha$ . The use of these agents – infliximab, in particular – has been associated with suppression of TNF- $\alpha$ -mediated granulomatous responses, leading to exacerbation of pulmonary tuberculosis, possible exacerbation of demyelinating central nervous system disease, and immunosuppression, leading to increased risk of serious infection and possibly decreased immunosurveillance against malignancy [108]. Since TNF- $\alpha$  appears to be a key mediator of granuloma development in sarcoidosis [108,109], these biologic treatments have been employed to treat isolated cases of cutaneous sarcoidosis. There are no RCTs or systematic reviews of the role of biologic anti-TNF- $\alpha$  agents in the treatment of cutaneous sarcoidosis. Evidence regarding their efficacy has been presented in case series and case reports.

### Benefits

**Infliximab** Doty *et al.* reported significant improvement of cutaneous sarcoidosis in five patients and resolution in one patient among six patients with recalcitrant cutaneous disease after treatment with infliximab for cutaneous and/or visceral disease using conventional dosing regimens. Some of the patients received concomitant pred-

nisonone therapy. Infliximab was generally well tolerated in all patients. Noted adverse events included a drug reaction in one patient after several months of therapy, oral candidiasis in one patient, and angioimmunoblastic lymphoma in one patient [110]. Heffernan and Anadkat reported 90% clearance of severe recalcitrant cutaneous sarcoidosis in a 51-year-old African-American woman treated at weeks 0, 2, and 6 with 5 mg/kg of infliximab. She experienced no adverse events during therapy [111]. Haley *et al.* reported flattening of all cutaneous sarcoidosis lesions in a 39-year-old African-American man with severe and recalcitrant cutaneous sarcoidosis, after treatment at weeks 0, 2, and 6 with 5 mg/kg of infliximab and concomitant oral prednisone. Notably, prednisone alone was ineffective, and the prednisone dose was tapered significantly over the course of therapy with infliximab. The patient did not experience any adverse effects associated with infliximab therapy [108].

Baughman and Lower reported improvement in two patients with persistent recalcitrant lupus pernio after treatment with infliximab 5 mg/kg at weeks 2, 4, and 12, without any significant adverse events [112]. Mallbris *et al.* reported substantial clinical improvement of severe recalcitrant cutaneous sarcoidosis in a 39-year-old white man after 5 mg/kg treatment with infliximab at weeks 0, 2, 4, 6, and 14 when combined with concomitant methotrexate administration to prevent anti-infliximab antibody production. Notably, methotrexate alone did not produce any clinical effect. The clinical effect of infliximab therapy was noticeable after the first treatment, and became significant after the fourth treatment. The patient experienced no adverse effects [109]. Meyerle and Shorr reported complete resolution of cutaneous sarcoidosis in a female patient after initiation of infliximab [113]. Pritchard and Nadarajah reported rapid resolution of cutaneous sarcoidosis in a 32-year-old white woman with multiorgan involvement. Skin nodules disappeared after 2 days of infliximab therapy. The authors reported no adverse effects, with the exception of infusion-associated complications [114]. Roberts *et al.* reported a single case of multisystem sarcoidosis with oculocutaneous improvement after infliximab [115]. Rosen and Doherty reported a single case with dramatic response with 3.5-year follow-up [116]. Sweiss *et al.* reported eight patients, two of whom had skin involvement, treated with infliximab, with the cutaneous disease improving in one and resolving in the other; treatment was well tolerated in all cases [117]. Saleh *et al.* used infliximab in 12 patients with multisystem disease, five of whom had skin disease; four of the five experienced improvement with infliximab [118]. Of the 12 patients, one died of a ruptured blood vessel and was found to have a plasma cell dyscrasia.

Baughman *et al.* conducted a large randomized study comparing placebo with infliximab at 3 or 5 mg/kg in 138 patients; skin disease was not specifically evaluated, but 19 of the patients had lupus pernio at baseline, with four of the patients who received 5 mg/kg responding, and none of the patients who received 3 mg/kg responding [119]. Therapy was generally well tolerated throughout the study. In one large retrospective study, Stagaki *et al.* evaluated the treatment regimens of 54 patients with lupus pernio and noted that those treated with infliximab had a better response than other regimens used, with nine of 13 responding to therapy [120]. Sené *et al.* described nine patients with refractory cutaneous sarcoidosis treated with infliximab at 5 mg/kg, with varying infusion regimens, and noted excellent responses, with three patients demonstrating resolution, three demonstrating good response, and two others improving [121].

**Adalimumab** Philips *et al.* reported resolution of a severe ulcerative recalcitrant cutaneous sarcoidosis nodule in a 55-year-old white woman after a 9-week course of adalimumab 40 mg per week. The patient was concomitantly on prednisone, and the dosage was reduced progressively after initiation of adalimumab therapy. The patient experienced no adverse events [122]. Heffernan and Smith reported significant improvement of severe and ulcerating recalcitrant cutaneous sarcoidosis in an African-American woman after 10 weeks of treatment with adalimumab 40 mg weekly, with clinical effects readily apparent after five treatments. She was concomitantly being treated with hydroxychloroquine and pentoxifylline, which by themselves had no clinical effect. The patient experienced no adverse effects [123]. Judson reported one case of recalcitrant lupus pernio responding to adalimumab 40 mg subcutaneous injections weekly after 9 months of therapy [124].

**Etanercept** Khanna *et al.* reported significant improvement of cutaneous sarcoidosis in a 50-year-old African-American woman 2 months after the addition of etanercept 25 mg twice weekly to her regimen of prednisone, hydroxychloroquine, and methotrexate. Etanercept was discontinued transiently during treatment of cellulitis [125]. Tuchinda and Wong reported a single patient who partially responded to etanercept 50 mg twice weekly who had previously failed to respond to prednisone, hydroxychloroquine, and methotrexate [126].

### Harms

Complications of anti-TNF- $\alpha$  biologic agents include infusion reactions (with intravenously administered infliximab), injection reactions (with subcutaneously administered adalimumab and etanercept), exacerbation of preexisting tuberculosis, exacerbation of demyelinating neurologic disease, and immunosuppression that may lead to an increased risk of infection and decreased cancer immunosurveillance. Evaluation with a purified protein derivation test (and chest radiography if the test is positive) is therefore necessary before treatment is started, and a thorough history and physical are mandatory to elicit a prior or family history of demyelinating disorders, malignancies, and risk for malignancy [127].

### Comments/implications for clinical practice

The articles published to date describe numerous small retrospective studies demonstrating improvement in cutaneous sarcoidosis, including lupus pernio, treated with infliximab, two treated successfully with adalimumab, and one treated successfully with etanercept. The agents appear to be well tolerated, but are significantly immunosuppressive and may be associated with increased risk of internal malignancy. While this is insufficient evidence to conclude that anti-TNF- $\alpha$  biologic agents are beneficial for the treatment of cutaneous sarcoidosis, these reports suggest that biological anti-TNF- $\alpha$  agents might be useful as an alternative or additional therapy, particularly in extremely recalcitrant cases. RCTs will therefore be necessary in order to evaluate fully their efficacy and long-term safety in patients with cutaneous sarcoidosis. It should be noted that one prospective trial evaluating etanercept for pulmonary sarcoidosis was terminated due to excessive treatment failures and safety monitoring board conclusion that the risk/benefit ratio was insufficient to proceed with enrollment [128]; as a result of this and cases of TNF-inhibitor-induced granulomatous diseases [129], some physicians have stated that etanercept should generally not be used for sarcoidosis. Notably, there is an ongoing

randomized placebo-controlled study investigating the effect of adalimumab in cutaneous sarcoidosis (NCT00274352), and another to compare golimumab (a novel TNF inhibitor) or ustekinumab (an IL-12/23 inhibitor) with placebo (NCT00955279).

### Conclusions

A review of the available data on oral and systemic therapy in cutaneous sarcoidosis reveals a dearth of evidence-based medicine, underscoring the need for RCTs. Unfortunately, most RCTs have been performed on pulmonary or other organ disease with a scattering of them also looking at skin disease. However, these often have variable end points that are not standardized, and drawing conclusions concerning cutaneous sarcoidosis can be challenging. Although oral steroids have been “grandfathered in” as the first-line treatment, on the basis of many clinicians’ personal experiences with sarcoidosis, this therapy has not been formally evaluated or proven in appropriate clinical trials.

The reported evidence suggests that chloroquine or hydroxychloroquine, methotrexate, and thalidomide may be the most effective medications for the treatment of cutaneous sarcoidosis. All of these agents may represent a reasonable therapeutic option as an alternative or adjunct to oral steroids. Less-studied potential alternatives include biologic TNF- $\alpha$  inhibitors, mycophenolate mofetil, tetracyclines, allopurinol, FAEs, and apremilast. Agents such as azathioprine and cyclosporine lack any data in cutaneous sarcoidosis. While chlorambucil was reported in the 1990s to treat chronic multi-organ sarcoidosis, the drug’s side-effect profile limits its potential for cutaneous sarcoidosis [64].

Additional drugs reported as successful in case reports include tranilast, melatonin, clofazimine, mepacrine, levamisole, alefacept, colchicine, systemic tacrolimus, and mizoribine [130–140]. While less studied, biologic TNF- $\alpha$  inhibitors may represent a new era in evidenced-based medicine for cutaneous sarcoidosis, especially in recalcitrant cases, particularly lupus pernio.

### What are the effects of topical and physical therapeutic interventions in patients with cutaneous sarcoidosis?

#### Topical corticosteroids and intralesional injections

While topical corticosteroids and intralesional injections are often recommended as the first-line treatment for the cutaneous manifestations of sarcoidosis, owing to their anti-inflammatory properties [18,21,22,38], the evidence for their efficacy is scant and has been reported in case series and case reports [141–144].

#### Benefits

Recently, Jung and Roh demonstrated two of three patients with specific lesions of cutaneous sarcoidosis responded completely to intralesional injections of triamcinolone; however, no dosing regimen was described [36]. Yanardag *et al.* demonstrated improvement in seven patients treated with intralesional kenalog, though these patients were receiving concomitant oral corticosteroids [145]. There are scattered reports of single cases demonstrating response to varying doses of intralesional corticosteroids, ranging from 10 to 40 mg/mL injected at intervals from biweekly to monthly [146–148].

In a single case report, intralesional chloroquine was successfully used to treat one patient as well [149].

#### Harms

In general, topical or intralesional steroids may lead to hypopigmentation, skin atrophy, tachyphylaxis, or systemic absorption. No

major side effects have been reported in any of the above studies. Minimal bleeding from needle puncture and postinflammatory hypopigmentation and hyperpigmentation are additional risks of intralesional hydrocortisone injections [143,150].

#### **Comments/implications for clinical practice**

The articles published to date describe a limited number of patients with cutaneous sarcoidosis treated with intralesional injections or topical steroids. This is insufficient evidence to conclude that this therapy is beneficial for the treatment of cutaneous sarcoidosis. Large RCTs are therefore necessary to evaluate their efficacy and safety. However, many dermatologists still use these modalities as first-line therapy, owing to their general anti-inflammatory properties.

#### **Tacrolimus**

Topical tacrolimus, a novel immunosuppressive agent successfully used in atopic dermatitis, inhibits the production of TNF- $\alpha$  by T cells and macrophages, and inhibits hapten-induced production of Th1 cytokines by T cells [151]. Thus, it may suppress the formation of granulomas in cutaneous sarcoidosis.

#### **Benefits**

Katoh *et al.* reported on a 62-year-old woman with recalcitrant persistent sarcoidosis of the face that resolved after treatment with topical tacrolimus without any adverse effects [151]. Gutzmer *et al.* reported on a 56-year-old woman with recalcitrant cutaneous sarcoidosis of the face whose disease almost completely resolved after a 3-month course of topical tacrolimus [152]. Landers *et al.* reported almost complete resolution of persistent cutaneous sarcoidosis in an eyebrow tattoo of a 70-year-old woman after the addition of tacrolimus 0.1% ointment to oral prednisone [153]. Green noted partial resolution of a nasal lesion of sarcoidosis with tacrolimus ointment 0.1% bid for 3 months that failed initial topical steroids [154]. De Francesco *et al.* noted topical tacrolimus 0.1% twice daily cleared facial sarcoidosis lesions on the forehead after 3 months of use in a patient who had failed clobetasol ointment [155], and Vano-Galvan *et al.* reported a complete response to topical tacrolimus 0.1% twice daily in a lichenoid type of cutaneous sarcoid lesion after 2 months of treatment [156].

#### **Harms**

Topical tacrolimus appears to be a safe and well-tolerated medication, both in the six reported cases of cutaneous sarcoidosis and in more than 1.7 million patients, most with atopic dermatitis. The most common adverse effects are skin burning and pruritus. Topical tacrolimus is not associated with increased rates of infection or malignancy in comparison with topical steroids when used intermittently [157,158].

#### **Comments/implications for clinical practice**

The articles published to date describe six patients who were treated successfully with topical tacrolimus. This is insufficient evidence to conclude that this therapy is beneficial for the treatment of cutaneous sarcoidosis. Further RCTs will be necessary in order to evaluate the safety and efficacy of topical tacrolimus in cutaneous sarcoidosis.

#### **Photomedicine**

##### **Flashlamp pulsed-dye laser therapy**

Flashlamp pulsed-dye laser (fPDL) therapy has been used successfully in the treatment of port-wine stains and telangiectasias, where

it selectively ablates the dilated and inflamed vessels [159]. This mechanism forms the rationale for its use in lupus pernio, a disfiguring cutaneous manifestation of sarcoidosis.

**Benefits** There are no RCTs or systematic reviews of fPDL therapy in cutaneous sarcoidosis. Goodman and Alpern reported on a woman with a 5-year history of lupus pernio of the nose who responded to fPDL at an energy level of 7–8 J/cm<sup>2</sup>. The improvement induced by the laser was temporary; the erythema and papules returned 7 months after the first treatment and 6–15 months after the second treatment, but on both occasions responded again to laser therapy. She received three sessions altogether, without side effects (such as atrophy, scarring, or hypopigmentation) [159]. Cliff *et al.* reported on a patient with lupus pernio of the nose, who improved after six treatment sessions at 6-week intervals with fPDL at a setting of 5.6–7.3 J/cm<sup>2</sup>. A biopsy of her nose after treatment showed noncaseating sarcoid granulomas, leading the authors to conclude that laser therapy was effective in improving the appearance of the lesions, but not the underlying disease process [160]. Dosik and Ashinoff reported on a woman with a 3-year history of topical and intralesional steroid-resistant lupus pernio who responded successfully to fPDL at an energy of 7.25 J/cm<sup>2</sup>. The therapy was given for nine sessions at 1–2-month intervals [161]. Holzman *et al.* reported improvement in a child with scar sarcoidosis treated with pulsed dye laser at 7.6–7.8 J/cm<sup>2</sup> fluence after three treatments at 6-week intervals. The patient previously failed topical tacrolimus and intralesional steroids [162]. Roos *et al.* had success with minimal use of fPDL (6 J/cm<sup>2</sup> fluence) being successful for multiple lesions of cutaneous sarcoidosis in a single patient [163].

**Harms** There were no side effects of laser therapy in the above patients. However, laser treatment has been reported to exacerbate cutaneous sarcoidosis in one patient [164]. The inherent risks of fPDL include erythema, atrophy, scarring, dyspigmentation, and a risk of eye damage when appropriate protection is not provided.

**Comments/implications for clinical practice** The articles published to date describe experience with six patients with treatment-resistant chronic lupus pernio who were treated with fPDL, three of whom had a positive result. This is insufficient evidence to conclude that fPDL is beneficial in the treatment of cutaneous sarcoidosis. RCTs will be necessary for definitive proof.

#### **Other laser modalities**

**Benefits** Nonablative lasers, such as a Q-switched ruby laser, that have the capacity to target foreign material in sarcoid lesions may be effective in treating cutaneous sarcoid lesions where foreign material, such as a tattoo, may be the nidus of granuloma formation. Additionally, ablative modalities, such as carbon dioxide laser, may effectively remove granulomatous lesions.

Grema *et al.* reported successful resolution of recalcitrant scar sarcoidosis of the elbow and knees in a 50-year-old woman using a Q-switched ruby laser. The patient remained recurrence free for over 3 years. The affected areas also had traumatic tattoos from abrasions, and did not resolve after three previous treatments with pulsed-dye laser [165]. O'Donoghue and Barlow reported on three patients with significant improvement of disfiguring lupus pernio after treatment with a CO<sub>2</sub> laser. The sarcoid granulomas were debulked, and wound healing occurred after 4 weeks. Two of the patients remained disease free after therapy [166]. Stack *et al.*

reported successful resolution of recalcitrant lupus pernio in a 31-year-old African-American man after excision and fulguration with a CO<sub>2</sub> laser, followed with an intralesional steroid injection in the postoperative period. The site healed well, and the patient had no recurrence. He experienced no adverse effects [167]. Young *et al.* reported on two patients with long-standing recalcitrant lupus pernio who were successfully treated with CO<sub>2</sub> laser resurfacing [168]. Ekback and Molin reported complete healing of long-standing recalcitrant lupus pernio in a 57-year-old white woman after two treatments with a frequency-doubled Nd:YAG laser (532 nm, 50 ms, 12–16 J/cm<sup>2</sup>) 7 months apart. Side effects included slight erythema and swelling of the treated skin areas 1 day after treatment. The patient had not experienced a relapse at the 3-month follow-up [169]. Rosende *et al.* reported the use of intense pulsed light therapy (515–1200 nm at 45 J/cm<sup>2</sup> fluence) over 2 years for control of a patient's lupus pernio; that patient had previously failed to respond to intralesional steroids and systemic agents (hydroxychloroquine, methotrexate, and allopurinol) [170]. Hocar *et al.* reported the successful use of a KTP laser (13 J/m<sup>2</sup>, 22 J/m<sup>2</sup> fluence) in two patients with facial cutaneous sarcoidosis [171].

**Harms** No significant complications were noted in these reports, but the inherent risks of laser therapy (scarring, dyspigmentation, erythema, as well as exacerbation of sarcoidosis and other photodermatoses) should be considered.

**Comments/implications for clinical practice** The articles published to date describe one patient who was successfully treated with a Q-switched ruby laser, six patients who were successfully treated with a CO<sub>2</sub> laser, one patient who was treated successfully with a frequency-doubled Nd:YAG laser, and two with a KTP laser. This is insufficient evidence to conclude that either therapy is beneficial for the treatment of cutaneous sarcoidosis. Further RCTs will be necessary in order to evaluate the safety and efficacy of laser therapy in cutaneous sarcoidosis.

#### Ultraviolet A therapy

Ultraviolet A1 (UVA1, 340–440 nm) has many known immunomodulating and immunosuppressive effects that may be responsible for the therapeutic effect in cutaneous inflammatory diseases, such as atopic dermatitis, urticaria pigmentosa, and lichenoid graft-versus-host disease. Longwave UVA induces apoptosis in T cells. UVA1 irradiation, similar to ultraviolet B, has been shown to induce the expression of immunosuppressive cytokines in human keratinocytes, including TNF- $\alpha$  and IL-10 [172,173]. The immunosuppressive properties of UVA1 form the basis for its use in cutaneous sarcoidosis.

#### Benefits

Mahnke *et al.* reported the disappearance of nearly all lesions of generalized recalcitrant cutaneous sarcoidosis in an 82-year-old white female after 50 sessions of medium-dose UVA1. Treatment was started at four times per week with medium-dose UVA1 at 20 J/cm<sup>2</sup> for the first three treatment sessions and 40 J/cm<sup>2</sup> for the subsequent 12 sessions. The final dose of 60 J/cm<sup>2</sup> was given 35 times. The patient experienced no adverse effects during or after therapy [172]. Graefe *et al.* reported marked improvement of cutaneous sarcoidosis on the forehead in a 63-year-old white woman after 25 sessions of high-dose UVA1, starting with 20 J/cm<sup>2</sup> for 2 days, 50 J/cm<sup>2</sup> for 3 days, 90 J/cm<sup>2</sup> for 5 days, and finishing with the final dose of 130 J/cm<sup>2</sup> four times weekly. After 25 sessions, a total dose of

2460 J/cm<sup>2</sup> was administered. The patient had no adverse effects and did not relapse [173].

Additionally, Patterson and Fitzwater reported significant improvement of hypopigmented sarcoidosis of the face after 8 months of tri-weekly psoralen-UVA (PUVA) therapy [174]. Courtois *et al.* also noted improvement in a single patient with cutaneous sarcoidosis with PUVA as well [175]. Gleeson *et al.* reported treatment of sarcoidosis with psoralen topical gel and UVA phototherapy. Six patients were given methoxypsoralen-8 gel 0.005% followed by 0.2 J/cm<sup>2</sup> with 0.1–0.2 J/cm<sup>2</sup> based on tolerance to a maximum of 3.7 J/cm<sup>2</sup> in conjunction with prednisone or hydroxychloroquine. All patients had skin improvement, with three of six obtaining complete resolution [176].

#### Harms

The patients experienced no adverse effects during therapy, but the long-term effects of UVA, such as the carcinogenic effects of therapy, have to be considered.

#### Comments/implications for clinical practice

To date, only two patients successfully treated for cutaneous sarcoidosis with UVA1 and eight patients successfully treated with PUVA have been reported in the literature. This is insufficient evidence to recommend UVA1 or PUVA therapy for cutaneous sarcoidosis. RCTs are therefore necessary to evaluate the efficacy and safety of UVA1 and PUVA in cutaneous sarcoidosis.

#### Photodynamic therapy

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) targets rapidly proliferating cells, leading to cytotoxic and immunomodulatory effects. PDT with topical ALA is currently approved for the treatment of actinic keratoses, but has also been used successfully to treat superficial basal cell carcinoma and Bowen's disease, as well as inflammatory conditions such as verrucae, scleroderma, and psoriasis [177]. The anti-inflammatory and immunomodulatory effects of PDT in skin form the rationale for its use in cutaneous sarcoidosis.

**Benefits** Karrer *et al.* reported the only use of PDT in cutaneous sarcoidosis [177]. A 3-month course of PDT with topical ALA produced complete resolution of recalcitrant cutaneous lesions that had persisted for 17 years in a 67-year-old white woman. Topical ALA 3% in a gel containing 40% dimethyl sulfoxide was applied, under occlusion with a light-impenetrant paper, to the affected areas for 6 h. Subsequently, the lesions were irradiated with an incoherent light source emitting wavelengths of 580–740 nm, with a light intensity of 40 mW/cm<sup>2</sup> and an energy density of 20 J/cm<sup>2</sup>. PDT was performed twice weekly for the first 8 weeks, followed by treatments once a week, for a total of 22 treatments in 3 months. Four weeks after the onset of therapy, the plaques flattened and faded. After 3 months, the skin lesions resolved completely, without the development of new lesions. A biopsy obtained from a former lesional site 4 months after therapy showed histologically normal skin. The patient was free of skin disease and visceral involvement 18 months after PDT. Wilsmann-Theis *et al.* reported resolution of auricular and periocular sarcoidosis lesions with application of methyl aminolevulinate for 3 h followed by broadband light (590–780 nm at 38 J/cm<sup>2</sup> for 20 min) for the auricular lesion and red light (630 nm at 37 J/cm<sup>2</sup> for 8 min) for the periocular lesions over eight treatment sessions. The patient was able to complete treatment, but the course was complicated by development of cutaneous erosion



and superinfection at the site [178]. Patterson treated a patient with a forehead plaque of sarcoidosis successfully with seven sessions of 5-ALA followed by a noncoherent light source (633 nm at 75 J/cm<sup>2</sup>) over a course of 16 months, noting minimal discomfort to the patient [179]. Penrose *et al.* used a 2-h application under occlusion of 20% 5-ALA followed by blue light (417 nm at 10 J/cm<sup>2</sup> for 16 min and 40 s) to resolve nasal sarcoidosis. The patient experienced some dyschromia and desquamation with treatments [180]. Hasegawa *et al.* used a 3-h application of 20% 5-aminolevulinic cream to facial sarcoidosis followed by intense pulsed light (640 nm at 22–24 J/cm<sup>2</sup>) which led to resolution with five sessions every 2 weeks [181].

**Harms** The adverse effects included a slight burning sensation during irradiation, followed by erythema and edema of the treated area, lasting for about 2 days. Slight hyperpigmentation of the treated area occurred after 2 weeks of treatment and persisted for about 3 months after the end of PDT [177]. In addition to dyschromia, Penrose *et al.* noted desquamation, while Wilsman-Theis *et al.* noted erosion with superinfection from their treatment modality [178,180].

**Comments/implications for clinical practice** To date, six patients with cutaneous sarcoidosis have been reported with a positive result to PDT. This is insufficient evidence to conclude that this therapy is beneficial for the treatment of cutaneous sarcoidosis. RCTs will therefore be necessary for definitive proof.

## Plastic surgery

### Benefits

There are no RCTs or systematic reviews of plastic surgery in the treatment of cutaneous sarcoidosis. In 1970, O'Brien described two patients successfully treated with plastic surgery for lupus pernio [182]. In 1984, Shaw *et al.* described a man with a 6-year history of treatment-resistant lupus pernio successfully treated with surgical excision and split skin grafting; the results remained good 2.5 years after surgery [183]. Collison *et al.* described a man with extensive ulcerative nodules of the lower extremities, which were resistant to topical/intralesional steroids, oral steroids, hydroxychloroquine, and methotrexate. He was treated with vigorous operative debridement and partial-thickness skin grafting. While the grafts were well accepted (80%), the patient developed new ulcerating nodules in previously uninvolved skin 2 months after surgery [184]. Streit *et al.* reported on a woman with widespread ulcerative cutaneous sarcoidosis who was treated with Apligraf (graft skin), a bilayered human skin equivalent, with good results [185]. Smith *et al.* reported a successful case of nasal resurfacing of lupus pernio by forehead flap rhinoplasty [186]. Preminger *et al.* reported one case of cutaneous nasal sarcoidosis that remained in remission at 7-year follow-up from surgical treatment [187]. Lesavoy *et al.* noted a case in which a simple and straightforward surgical approach to severe nasal deformity from sarcoidosis obtained excellent results [188].

### Harms

No complications were noted in the above studies. However, the inherent risks of general anesthesia and surgery (bleeding, scarring, postoperative infection) should be considered.

### Comments/implications for clinical practice

The above articles describe eight patients with treatment-resistant chronic lupus pernio who were treated with plastic surgery, all of whom had a positive result. This is insufficient evidence to conclude

that this therapy is beneficial in the treatment of cutaneous sarcoidosis.

## Conclusions

There is a lack of significant evidence-based data on topical and physical therapies for cutaneous sarcoidosis. There are no RCTs to prove that intralesional or topical steroids are effective in the treatment of cutaneous sarcoidosis. Intralesional and topical steroids, like oral steroids, have been accepted as first-line therapies on the basis of clinicians' experience, with no definitive dosage or duration of therapy identified. Topical tacrolimus, a nonsteroidal agent, has been reported as successful therapy in only six patients. The physical modalities of laser and plastic surgery, as well as UVA phototherapy and PDT, have been reported as successful in treatment-resistant cases and disfiguring nasal sarcoidosis, but larger studies are lacking. Phonophoresis is another potentially beneficial modality, but it has only been described in an isolated case report [189]. Radiation therapy has been used in limited cases [190,191].

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### Key points

- There are no RCTs of any therapy for the treatment of cutaneous sarcoidosis.
- In a review of the existing literature on nonsteroidal systemic therapies for cutaneous sarcoidosis, antimalarials, methotrexate, and thalidomide appear to show clinical benefit, and thus may represent a reasonable therapeutic option in patients requiring an additional or alternative therapy. Other medications, such as biologic TNF inhibitors, tetracyclines, allopurinol, FAE, leflunomide, and apremilast require additional study, but could be used in difficult or resistant cases.
- A review of the existing literature on topical and physical therapies for cutaneous sarcoidosis shows that no therapy has been proven effective in controlled trials. However, the use of topical and intralesional corticosteroids, topical tacrolimus, photodynamic therapy, lasers, and plastic surgery could be used in certain clinical situations.

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## CHAPTER 67

# Erythema multiforme

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## Background

### Definition

Erythema multiforme (EM) is an acute, febrile, self-limited, eruption characterized by target cutaneous lesions, with a symmetric and mainly acral distribution. Lesions are annular, with three zones: a central area of dusky erythema, sometimes bullous, a middle paler zone of edema, and an outer ring of erythema with a well-defined edge. Face and limbs, especially hands and feet, are the most commonly affected areas and are sometimes selectively involved. Mucous membrane erosions are frequent and define EM major or majus (EMM), compared with EM minor which lacks mucous membrane involvement. Histopathological examination typically shows an interface infiltrate and limited epidermal necrosis that affects mainly the basal layer. Some confusion persists in terminology and in the boundaries between EMM, Stevens–Johnson syndrome, and “EM-like” drug eruptions.

### Incidence

Unknown. For cases severe enough to require hospitalization: 1–6 per million per year.

### Etiology/risk factors

The principal cause is infection with herpes simplex virus (HSV), which probably accounts for 40–60% of all cases in adults. Many other infections can induce occasional cases, especially *Mycoplasma pneumoniae* infection, which is the leading cause in many pediatric series.

### Prognosis

EM has low morbidity and no mortality. Spontaneous resolution comes in 1–6 weeks. Sequelae are rare, but mucous membranes, including eyes and bronchial tract, may be affected in severe cases of EMM. Recurrences are frequent (at least 30%). Rarely recurrences overlap, leading to “continuous” or “persistent” EM. Mouth erosions may strongly impair the quality of life of patients.

### Aims

To reduce the duration of fever, eruption, and hospitalization; and to prevent or reduce recurrences.

### Outcomes

Duration of fever, eruption and hospitalization; frequency of recurrences; number of days with symptoms per year.

### Methods

*Clinical Evidence* search and appraisal October 2012 (Cochrane databases of randomized controlled trials (RCTs) and controlled clinical trials, Medline 1966 to October 2012).

We found one brief “evidence-based” review on corticosteroids [1] and six randomized clinical trials, all on a small number of patients and most raising concerns on methodological issues [2–7].

## Questions

### What are the effects of treatment of acute attack?

#### Short course of systemic corticosteroids

Based on a retrospective series or small RCT, corticosteroids seem to shorten the duration of fever and eruption but to increase length of hospitalization because of the risk of complication. There is no evidence that patients with EM benefit from corticosteroids.

#### Benefits

Sixteen children with EMM were included in a randomized controlled prospective study within 3 days from the onset of rash; 10 received bolus infusions of methylprednisolone (4 mg/kg per day) while six had only supportive treatment (in a different center). Corticosteroids allowed a significant reduction of the period of fever (4.0 vs 9.5 days), but not a significant reduction of the period of acute eruption (7.0 vs 9.8 days) and milder signs of prostration. Complications were minimal in both groups [7].

**Harms**

An RCT included nine adult patients with mild, uncomplicated EMM; four received prednisolone and five received placebo. The mean length of stay in hospital was longer in the corticosteroid group (9.5 vs 8 days). But diagnoses were not clear: histology was consistent with EM; a drug was suspected in five cases; and no information about HSV was given [5].

In a retrospective study, Rasmussen compared 17 children with EM treated by systemic corticosteroids with 15 children with supportive care only. Both groups were comparable in age, sex, length of prodroms, exposure to drugs, initial fever, extent of oral and cutaneous involvement, and frequency of isolation of pathogens. The group with corticosteroids had a shorter fever period (1.8 vs 5.5 days) but a longer mean length of hospitalization (21 vs 13 days), because of more frequent complications (53% vs 0%) [8].

In a series of 51 children, corticosteroids were claimed to worsen the prognosis: the patients treated with corticosteroids had 74% of complications, versus 28% for the patients without corticosteroids [9].

In a series of 25 patients with EM minor, corticosteroids allowed no clinical improvement except a shorter duration of fever (2.7 vs 5.6 days) [4].

**Comment**

The usefulness of corticosteroids seems to be limited, and side effects are frequent. However, the methodology of most studies was poor, with small numbers, and a mix of idiopathic or viral-associated EM and drug-induced Stevens–Johnson syndrome.

**Erythromycin**

We found no evidence on usefulness of erythromycin.

**Benefits**

We found no evidence.

**Harms**

We found no evidence.

**Comment**

Erythromycin or related antibiotics are claimed to be potentially useful only when *Mycoplasma pneumoniae* infection is suspected. There is no evidence to support that treating the infection has a beneficial effect on the course of EM.

**Acyclovir**

We found no RCT. In several series it was reported that initiating acyclovir for the treatment of full-blown post-herpetic EM was useless.

**Benefits**

We found no evidence.

**Harms**

We found no evidence.

**Comment**

Probably useless (strength of recommendation C; recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening).

**What are the effects of treatment to prevent recurrence?****Sun protection**

We found some indirect evidence on possible benefit of sun protection.

**Benefits**

Ultraviolet A may induce herpes recurrence. We found some evidence that sunscreen protection prevents herpes recurrence (strength of recommendation B?) [10]. We found no data on possible effect on recurrent EM.

**Acyclovir**

We found one RCT, on the effectiveness of continuous oral acyclovir to prevent EM recurrences.

**Benefits**

We found one RCT: 19 patients with more than four attacks of EM per year were enrolled in a 6-month double-blind, placebo-controlled trial of acyclovir 400 mg twice daily. Median number of attacks in the acyclovir group was zero (0–2) compared with three (1–6) in the placebo group (significantly different). At inclusion time, five patients had not clinical evidence of disease precipitation by HSV; two of them were in the acyclovir group; one showed complete disease suppression [6].

A prior RCT had observed no efficacy from topical acyclovir at the site of recurrent herpes [3].

**Harms**

We found no evidence.

**Comment**

Continuous oral acyclovir is effective to prevent recurrences of herpes-associated EM, but it may also be useful in some patients without clinical evidence that herpes is the precipitating factor (strength of recommendation B).

Valaciclovir and famciclovir have not been evaluated in formal trials but series suggested that they are able to prevent recurrences, likely as well as acyclovir [11] (strength of recommendation C).

**Levamisole**

In one RCT, levamisole appeared useful.

**Benefits**

We found a double-blind, placebo-controlled crossover trial, which included 14 patients with chronic or recurrent EM resistant to corticosteroids. Dose of levamisole was 150 mg/day for three consecutive days each week, for at least 4 weeks after first appearance of a lesion. Levamisole allowed decrease of severity, duration, and frequency of EM attacks [2].

An open comparative trial showed similar efficacy of levamisole used alone (17 patients; 76% of complete response) versus prednisone–levamisole combination (22 patients; 82% of complete response) [12].

**Harms**

Because agranulocytosis is a severe and not exceptional adverse effect, levamisole is not approved by most drug agencies.

**Comment**

The benefit–risk balance does not support the use of levamisole in EM (strength of recommendation C).

### Azathioprine, mycophenolate mofetil

We found several case series reporting benefit of azathioprine.

#### Benefits

We found no controlled trial.

In a series of 65 patients with recurrent EM, 11 were treated by azathioprine, when all other treatments had failed. Azathioprine was successfully used in all 11 patients [13]. Another case series reported five cases [14].

In a series of 48 cases both azathioprine and mycophenolate mofetil were reported to induce complete or partial remissions [11].

#### Harms

No evidence of harm was reported in these case series. Most immunosuppressive agents are associated with increased susceptibility to infection and with the development of malignancies. Baseline erythrocyte thiopurine methyltransferase levels should be checked prior to initiating treatment with azathioprine. Blood counts and liver function should be carefully monitored. Mycophenolate mofetil commonly causes gastrointestinal symptoms and has been rarely reported to cause lymphoma and recently multifocal leukoencephalopathy.

#### Other agents

We found no controlled trials.

Series reported benefits from dapsone, hydroxychloroquine, intravenous immunoglobulin, potassium iodide, or thalidomide [11,15].

### What are the effects of treatments on “continuous” or “persistent” forms?

#### Thalidomide

We found one case series on the benefit of thalidomide in EM.

#### Benefits

We found one retrospective analysis of thalidomide prescriptions (1981–1993), which showed efficacy for treatment of recurrent or “continuous” EM [16]. These data were uncontrolled and only supported by further case reports.

#### Harms

We found no evidence, but well-known severe side effects of thalidomide, especially teratogenicity and toxicity to nerves, deserve careful attention.

#### Comment

Likely useful, based on clinical “expert opinion” only (strength of recommendation C).

### Key points

- We found one RCT, which provided evidence for the usefulness of acyclovir to prevent EM recurrences (strength of recommendation B; recommendation based on inconsistent or limited-quality patient-oriented evidence).
- We found no evidence on usefulness of systemic corticosteroids in treatment of acute attack of EM.
- We found no good evidence on all other therapeutic choices.

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### Interventions

#### Beneficial

- Systemic acyclovir to prevent recurrence.

#### Trade-off between benefits and harms

- Levamisole, thalidomide.

#### Unknown effectiveness

- Antimalarials, azathioprine, dapsone, mycophenolate mofetil, potassium iodide.

# Stevens–Johnson syndrome and toxic epidermal necrolysis

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## Background

### Definition

The definitions proposed by the “consensus of experts” in 1993 [1] were more or less clearly accepted worldwide. According to these definitions, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are variants of the same process, presenting as severe mucosal erosions with widespread purple cutaneous macules (or “atypical targets”), often confluent with a positive Nikolsky sign and epidermal detachment. In SJS, epidermal detachment involves less than 10% of total body skin area; transitional SJS–TEN is defined by an epidermal detachment between 10 and 29% and TEN by a detachment of 30% or more. Full-thickness epidermal necrosis is observed on pathological examination. The skin biopsy and occasionally a direct immunofluorescence test are necessary to exclude alternative diagnoses of diseases that may resemble SJS/TEN. No laboratory test or imaging technique is needed for the diagnosis, but many are needed for evaluation of complications and occasionally for determination of causality.

### Incidence

Based on cases registries and observational studies, the incidence of TEN is estimated to 1–1.4 cases per million inhabitants per year. The incidence of SJS is probably of the same order (1–2 cases per million inhabitants per year) [2–4].

Women are overrepresented among adult cases, whereas the sex ratio is equal in childhood. The incidence increases after 40 years of age.

### Etiology/risk factors

SJS/TEN is predominantly drug induced (70–80% of cases). Graft-versus-host disease is another well-established but rare cause, independent of drugs. A few cases are related to infections (*Mycoplasma*

*pneumoniae*); other cases remain unexplained (“idiopathic” forms). The most extensive studies of medication use and SJS/TEN mainly pointed to allopurinol, many anticonvulsants (lamotrigine, carbamazepine, phenytoin, phenobarbital), anti-infectious sulfonamides, and some nonsteroidal anti-inflammatory drugs [5,6]. Human immunodeficiency virus infection, “collagen-vascular diseases,” especially systemic lupus, active cancer, and radiotherapy increase the risk [5,6]. A genetic susceptibility human leukocyte antigen (HLA)-linked has been demonstrated for a few drugs, varying with ethnicity (see later).

### Prognosis

SJS/TEN is an acute, self-limited disease, but with high morbidity and nearly constant sequelae. Mortality rates at 3 months are 10–15% with SJS, 40–50% with TEN, and 30–35% with transitional forms [7]. Epidermal detachment may be extensive and may extend to the entire skin surface in the most severe cases. As in severe burns, fluid losses are massive and electrolyte imbalance common. Super-infection, thermoregulation impairment, energy expenditure, alteration of immunologic functions, and hematologic abnormalities are usual systemic complications. Mucous membrane involvement (oropharynx, eyes, genitalia, and anus) require attentive nursing. Gastrointestinal and tracheobronchial epithelium can be also involved and cause high morbidity.

Age, recent malignancy, percentage of denuded skin, neutropenia, serum urea nitrogen level, and visceral involvement are prognosis factors. SCORTEN, a SJS/TEN-specific scoring system for vital prognosis estimation, has been proposed [8]. SCORTEN has been validated in many centers [9–15].

After healing of the acute phase (3–6 weeks), nearly all patients suffer from one or several sequelae that alter their quality of life and may be severely invalidating. They include pigmentation disorders, scars on skin, synechiae and dryness of mucous membranes of the



mouth and genitalia, posttraumatic stress, and many others. The most severe are ocular lesions that may progress and lead to blindness [13].

### Aims of treatment

- *In the acute stage:* to reduce mortality, to limit the extent of the disease, to reduce associated morbidity, and to prevent sequelae.
- *In the long term:* to detect and manage sequelae, to evaluate drug causality, and to advise the patient on future utilization of medicines.

### Outcomes

In a disease of such severity the primary outcome is obviously *mortality rate*; secondary outcomes include percentage of epidermal detachment at the acme of the disease, infectious complications, length of healing, length of stay in hospital, and sequelae.

### Methods

For search and appraisal we used the Cochrane Library and Medline 1966 to June 2012. We found:

- Three systematic reviews of “specific” treatments [16–18].
- Thirteen randomized controlled trials (RCTs):
  - seven that only mentioned the occurrence of SJS/TEN as a side effect during an RCT (not analyzed);
  - one evaluating corticosteroids in erythema multiforme (not analyzed);
  - one specifically evaluated treatment of SJS/TEN with thalidomide [19];
  - four addressed the treatment of ocular lesions caused by a variety of diseases; all included a minority of SJS/TEN cases [20–23].
- Two treatment recommendations based on adequate methodology [24,25].
- One large observational study (cohort) [7].

## Questions

### Is it possible to prevent Stevens–Johnson syndrome/toxic epidermal necrolysis?

#### Pharmacogenetics approach

In the past 10 years many studies have addressed the possible genetic basis of severe adverse drug reactions, and especially SJS/TEN. A Taiwanese group first reported a 100% association between SJS/TEN induced by carbamazepine and HLA-B\*15:02 [26] and also a 100% association of SJS/TEN induced by allopurinol and HLA-B\*58:01 [27]. Many further studies were done, and 2012 knowledge on HLA as possible marker of SJS/TEN can be summarized as follows:

- A strong association of carbamazepine-related SJS/TEN to HLA-B\*15:02 was found only in Asian countries where this allele has a high prevalence (China, Singapore, Thailand, Vietnam, India, etc.), but not in Japan, Korea, or Europe [28].
- The association of HLA-B\*58:01 and SJS/TEN related to allopurinol is found worldwide but is much less strong than in South East Asia [28].
- In Han Chinese, HLA-B\*15:02 is also a risk factor for induction of SJS/TEN by other “aromatic” anticonvulsants (phenytoin,

oxcarbazepine, lamotrigine). The association is weaker than for carbamazepine, however [29].

- Even in Taiwan, most persons with the HLA-B\*15:02 allele do not develop SJS/TEN when treated with carbamazepine, probably because the reaction of the immune system also requires specific allele(s) in the repertoire of T lymphocytes [30].
- No other association strong enough to be useful as a predictive test has been detected [31].

A large cohort study has demonstrated the absence of SJS/TEN in 4505 Taiwanese patients who tested negative for HLA-B\*15:02 and were treated with carbamazepine [32]. *That study is the first evidence that SJS/TEN can be prevented by a pharmacogenetics approach.*

Based on the above evidence, drug agencies in USA (Food and Drug Administration) and Europe (European Medicines Agency) have issued the recommendation that “patients originating from areas where HLA-B\*15:02 is prevalent [China and South East Asia] should be offered a test for that allele before being treated with carbamazepine.”

In patients positive for HLA-B\*15:02 it is also logical to avoid all “aromatic anticonvulsants” as alternatives to carbamazepine. Testing patients from South East Asia for HLA-B\*58:01 before prescribing allopurinol also seems logical [33], even though no recommendation has been issued yet by drug agencies. Although knowledge on the genetics of SJS/TEN is still limited, it appears also prudent to avoid the “culprit” drug in first-degree relatives of a patient who developed SJS or TEN.

### Avoiding prescription of “strongly associated” medications that lack evidence of usefulness

Some medications “strongly associated” with the development of SJS/TEN are too often prescribed without an evidence-based rationale. For example, there is no evidence that prophylactic anticonvulsant therapy decreases the incidence of seizures in patients with brain tumor and no history of seizures [34], a practice that is associated with many cases of SJS/TEN related to anticonvulsants [6]. There are persistent controversies on potential benefits of allopurinol use in patients with asymptomatic hyperuricemia, which was the reason for prescription in a majority of patients with allopurinol-related SJS/TEN in Europe [35].

### What are the effects of prompt withdrawal of potential culprit drug(s)?

We found limited evidence that early withdrawal of the drugs that cause SJS/TEN improves the prognosis of the disease.

#### Benefits

One observational study, showed that death rates were lower when causative drugs with short elimination half-lives were withdrawn no later than the day when blisters or erosions first occurred: 2/44 (5%) versus 11/42 (26%). No difference was seen for drugs with long half-lives [36].

#### Harms

We found no data.

#### Comment

Since it would be unethical to perform an RCT of the effect of prolonging drug administration, observational studies will remain the only available clinical evidence for this question.

In addition to immediate discontinuation of suspected drug(s), stopping concomitant medications that are known for impairing

the metabolism or excretion of the suspect drug should be considered.

Discontinuation of other non-suspected important medications should be avoided (experts' recommendation [25]).

### Are there any specific treatments?

The mechanism leading to apoptosis of the epidermis and mucous membranes epithelium in SJS/TEN has been suspected for years to involve the immune system but was elucidated more precisely in the past few years. Basically, it involves drug-specific cytotoxic T-cells and nonspecific cytotoxic cells that release cytolytic cytokines, especially granulysin [37].

A long list of medications/methods expected to have an immunosuppressive or immunomodulating effect were proposed (e.g., corticosteroids, cyclophosphamide, plasmapheresis, thalidomide, *N*-acetylcysteine, intravenous human immunoglobulins (IVIGs), cyclosporine A, and anti-TNF monoclonal antibodies). We will only discuss here those that were submitted to some evaluation: thalidomide (RCT), IVIGs (meta-analyses, cohort), corticosteroids (meta-analyses, cohort), cyclosporine A (comparison of observed mortality with mortality predicted by SCORTEN).

### Thalidomide

We found one RCT versus placebo, which shows an excess of mortality with thalidomide.

Thalidomide has been proposed as treatment of TEN because it is a potent inhibitor of TNF- $\alpha$  action.

### Benefits

We found no clinical evidence about benefits of thalidomide use in TEN/SJS.

### Harms

We found a double-blind, randomized, placebo-controlled study of thalidomide in TEN [19]. The regimen was a 5-day course of thalidomide 400 mg daily. Twenty-two patients were included, but the study was stopped because there was an unexplained excess of mortality in the thalidomide group (10 of 12 patients died, compared with 3 of 10 in the placebo group). There was no significant difference in origin of death between both groups [19].

### Comment

Based on a unique RCT, thalidomide should not be used in TEN.

### Intravenous immunoglobulins

Using IVIGs for SJS/TEN was proposed in 1998 [38] based on the hypothesis that Fas ligand (FasL) was the main mediator of widespread keratinocyte apoptosis in TEN and on the finding that high-dose IVIGs were able to antagonize FasL effects. More recent studies refuted an important role of FasL [39–41], invalidating the initial rationale for using IVIGs.

We found no good evidence on the effects on IVIGs in SJS/TEN, but available data do not suggest efficacy.

We found three "systematic reviews" [16–18].

- 1 Del Pozzo-Magana *et al.* [17]. The authors included 31 publications: 18 case reports (one to four cases), six prospective "cohorts" (2–10 cases), six retrospective "cohorts" (7–17 cases), and one "pseudo-randomized" study of erythema multiforme major (16 cases). "Cohort" studies adhered poorly to STROBE recommendations. Outcome measures were time to objective response (lack of fever), to remission (undefined), and length of hospital stay. Results are presented in a table as range of means of the

three time measures and many missing values by four treatment groups: IVIGs, corticosteroids, dressings, supportive care only. Based on a longer time to absence of fever (mean 9.5 days in a single study vs range of means 1–4 days) and to complete remission (7–22 vs 4–18 days), the authors conclude that supportive care alone is the "worst option" and that IVIGs or corticosteroids can be recommended. They do not discuss the nonspecific effect of corticosteroids on fever and the mild "difference" in time to complete remission. Poor quality and heterogeneity of reports did not allow any statistical analysis.

- 2 Roujeau and Bastuji-Garin [16]. This paper is another systematic review far from being perfect. Authors gathered all 47 series including at least 10 cases of SJS/TEN treated with any of the three following regimens: supportive care only, corticosteroids only, IVIGs only. Among these, all 13 containing a clear description of treatment(s) and an evaluation of SCORTEN were analyzed, allowing calculation for each series of a mortality ratio (MR: actual mortality/mortality predicted by SCORTEN) and a pooled MR with 95% confidence interval (CI) for each treatment. The series analyzed comprised a total of 439 patients. Supportive care only was used in 199 with a pooled MR of 0.89 (95% CI, 0.67–1.16;  $P = 0.43$ ) and IGIVs in 162 with a pooled MR of 0.82 (95% CI, 0.58–1.12;  $P = 0.23$ ).

These results suggested that SCORTEN slightly overestimated the risk of dying in both groups without any difference related to treatment.

- 3 Huang *et al.* [18]. This paper is far from being perfect because, in the absence of any RCT, the authors included what they called "observational controlled" series with at least eight cases of TEN or SJS–TEN overlap treated with IVIGs and compared with an historical group or comparing observed mortality with mortality predicted by the SCORTEN. A major difference with prior compilations of series [42] was effort to eliminate duplicate cases. They finally analyzed 17 studies including 113 patients treated with IVIGs and 130 treated with supportive measures only. The two groups were similar in ages and distribution of TEN versus overlap cases. The pooled odds ratio (OR) for mortality in patients treated with IVIGs was 1.00 (95% CI, 0.58–1.75). The authors also performed subgroup analyses that they interpreted as indicating a trend that higher doses of IVIGs might be better than low doses in adults and that IVIGs might be effective in children. Based on very low numbers, the later conclusion is highly debatable.

We found one European cohort study (EuroSCAR) [7]. A limitation is that an unknown number of patients had been likely included in series reporting the effect of a treatment in a few participating centers (IVIGs). The cohort included 281 patients, 87 received supportive treatment only, 35 IVIGs only, and 40 IVIGs and corticosteroids. Mortality did not differ between treatment groups, with no trend for a benefit from IVIGs (OR, 1.6; 95% CI, 0.6–4.3) compared with supportive care.

### Corticosteroids

We found no good evidence about corticosteroids use in SJS/TEN. Beneficial effects are doubtful.

We found two meta-analyses [16,17] and one cohort study [6], all also addressing the possible benefit of IVIGs. The first meta-analysis of pediatric cases suggested some debatable benefit on a shorter course of disease. The second meta-analysis included all series published up to December 2009 with at least 10 patients and using SCORTEN to compare actual with predicted mortality.

The pooled MR for 78 patients treated with corticosteroids was 0.92 (95% CI, 0.53–1.48), compared with 0.89 (95% CI, 0.68–1.16) for 199 patients with supportive care. That result does not suggest a substantial benefit.

The cohort included 281 patients. In the 119 who had received corticosteroids only, there was a trend towards a decreased mortality compared with supportive care that did not reach statistical significance (OR, 0.4; 95% CI, 0.2–1.1).

Many TEN cases have occurred during treatment by corticosteroids for preexistent disease. The possible impact on development of SJS/TEN was evaluated by three studies. The data of 216 patients with TEN were investigated in a retrospective study; 11 of them had been treated with corticosteroids for at least a week prior to the first sign of TEN (from 1 week to several months, at dosage between 7.5 and 325 mg prednisolone per day) [43]. In another series of 179 patients, 13 were undergoing long-term glucocorticosteroid therapy before TEN. Compared with 166 other cases, these patients had a longer delay between the introduction of the suspect drug and the onset of TEN, and a longer time elapsed between the first symptom of TEN and hospital admission. No other differences were observed [44].

Recently, a case-control analysis was done on the database of EuroSCAR and RegiSCAR studies comparing 92 patients with prior exposure to corticosteroids before the onset of SJS/TEN to 321 patients without prior exposure. In patients receiving corticosteroids the onset of disease after initiation of inducing drug was delayed by 7.1 days (95% CI, 0.2–4.5), disease progression was longer by 2.2 days (95% CI, 1.1–3.2), but disease severity and mortality were not affected [45].

#### Comment

These three studies of systemic corticosteroids use before onset of SJS/TEN obtained similar results, suggesting that corticosteroids have some impact on the progression of the disease, while strangely not modifying its final severity and mortality.

### Cyclosporine A

We found no sufficient evidence on effects of cyclosporine.

#### Benefits

We found several case reports and two case series of TEN treated with cyclosporine A.

In the first series of 11 cases of TEN [46], the treatment was safe and was associated with a more rapid re-epithelialization rate and a lower mortality rate (0/11 vs 3/6) in comparison with a historical series of patients treated with cyclophosphamide and corticosteroid.

The second series [47] included 29 patients with SJS or TEN treated with cyclosporine (3 mg/kg per day). None died when the SCORTEN predicted three deaths (no significant difference). Progression of disease was less frequent than among historical controls.

#### Harms

No serious side effects were reported in the first series [46] and three were reported in the second (reversible leukoencephalopathy, severe neutropenia, nosocomial pneumonitis) [47].

#### Comment

These results suggest that further studies should be conducted to evaluate the possible effectiveness of cyclosporine.

Conclusions on specific treatments (endorsed by recommendations issued in USA [24] and in France [25]):

- Available evidence does not allow recommending any “specific” treatment.
- Adequate supportive care is the priority in management of SJS/TEN.

### What are the effects of symptomatic treatments?

Most, but not all, of the symptomatic treatments for SJS/TEN are the same as those for severe burns. Some are based on evidence obtained in burns and/or in patients treated in intensive-care settings. We found no controlled study of supportive care for SJS/TEN.

Major components of symptomatic treatment include: (expert recommendations) [24,25]:

- Careful handling, strict asepsis.
- Warming of environmental temperature.
- Control of pain with liberal use of morphine or related agents.
- Intravenous fluid replacement (quantity adjusted daily) by venous lines as distant as possible from affected areas, with formulas decreased by at least one-third from formulas proposed for burns.
- Control of frequent hyperglycemia.
- Continuous enteral nutrition (by nasogastric tube).
- Local care of skin using antiseptics and nonadhesive dressings.
- Irrigation, emollients, antiseptic solutions without preservatives many times daily of affected mucous membranes; mechanical disruption of adhesions.
- Prophylactic use of antibiotics is *not* recommended.
- Repeated bacteriological sampling of skin, blood, urine, and site of intravenous lines.

Debridement of necrotic epidermis is highly controversial:

- Stripping of all “detachable” epidermis under general anesthesia is still performed in many burn units and recommended by some US experts [24]. That practice is based on an old RCT that demonstrated a benefit on survival for adult patients with *burns* of mixed thickness [48].
- If stripping is done, it must be followed with adequate coverage (porcine xenografts, cadaveric allografts, silver sulfadiazine/gauze dressings, amniotic membranes, cultured keratinocytes, synthetic dressings). Many RCTs compared these different dressings and suggested benefits for amniotic membranes or synthetic dressing versus conventional silver-sulfadiazine-impregnated gauze [49–53].
- In SJS/TEN, the level of epidermal detachment is equivalent to superficial burns (thickness I or IIa) and a growing number of burn units are using “anti-shear” therapy instead of stripping [54,55].

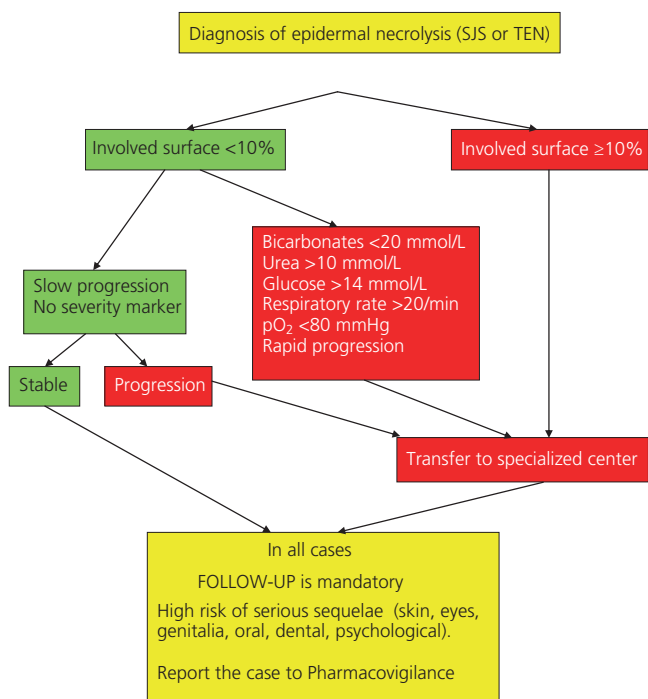
#### Comment

The supportive measures described above require specialized nurses and physicians (multidisciplinary team) and access to life-supporting resources such as mechanical ventilation, dialysis, and anesthesia.

### Is there a policy for referral to specialized medical units?

We found several large retrospective series that observed a lower risk of infection and a lower mortality if patients were referred early to a specialized unit [9,13,56–58].

None of these studies discussed a possible selection bias; that is, milder cases being less likely to be transferred. Most, anyhow, were



**Figure 68.1** Decisional tree for transfer of patients with SJS or TEN. We thank the French Haute Autorité de Santé (HAS) for allowing the translation from the original figure published within the Plan National de Diagnostic et de Soins “Nécrolyse épidermique toxique (Syndromes de Stevens-Johnson et de Lyell) – Juin 2010.” The HAS denies any responsibility for errors or omissions resulting from translation. For the original text, see Ref [25].

based on multivariate analyses, including factors known to impact the prognosis.

### Comment

Even if current evidence is far from being perfect, it suggests that delayed transfer is harmful.

Recommendations issued by experts in the USA and France consider that early referral to a specialized unit is a priority [24,25]. A decisional algorithm for referral was proposed in the French recommendations (Figure 68.1) [25].

### Evaluation of drug causality: are Stevens–Johnson syndrome/toxic epidermal necrolysis always drug induced?

Twenty years ago it was often stated that TEN was always drug induced while SJS could be induced by drugs or by infections [59]. Both parts of this assertion have proved erroneous with increasing knowledge. In the SCAR case–control study the etiologic fractions for significantly associated medications were 64%, 66%, and 65% for SJS, overlap SJS–TEN, and TEN respectively [60]. These were underestimates, since the statistical power was insufficient to prove an association for a few rarely used drugs, when found in a few cases and no control, but it was also unlikely that the etiologic fraction might increase to more than 80% with much larger studies. With further large studies looking for individual causality, a prob-

able or very probable drug cause was found in 62% of cases, and a possible drug cause in 23%. Fifteen percent of patients had been exposed either to no medication at all (2%) or only to medications with unlikely or very unlikely causality (13%) [61]. The very rare cases with a documented alternative etiology (acute graft-versus-host disease, *Mycoplasma pneumoniae* infection) explain a very small fraction of cases; others remain “idiopathic.”

### Is there any test to prove drug causality?

We found no evidence for a reliable test to prove the link between a single case and a specific drug.

### Benefits

A few studies about patch tests in SJS/TEN cases suggested a rather low sensitivity (10–60%), but probably good specificity, suggesting that they may help in assessing causality in some difficult cases [62,63].

We found only case reports and no clinical trial about in vitro tests (i.e., lymphocyte transformation tests) [64,65].

### Harms

No reactivation of SJS/TEN was reported from patch tests. We found only a few case reports of generalized erythema or irritation.

### Comment

Sensitivity and specificity of patch tests – and thus their clinical usefulness – need further evaluation, but available data suggest low sensitivity. The same conclusion also applies to available in vitro tests.

### Usefulness of algorithms for drug causality

Many methods have been proposed to determine causality of adverse drug reactions [66,67]. A specific algorithm (ALDEN) has been elaborated for SJS/TEN and showed an acceptable correlation with the results of case–control analyses and better performances than a general algorithm applying to all types of reactions [61].

### Benefits

ALDEN provides a better discrimination of “probable/very probable” and unlikely/very unlikely causative medications, allowing better counseling on future use of medications.

### Harms

We found no study of harm that may result from erroneous determination of causality.

### Is a follow-up needed?

Several hundred case reports focused on the many possible sequelae of SJS/TEN and their potential severity. Two cohort studies [13,68] demonstrated that sequelae were much more frequent than previously suspected, affecting more than 90% of patients surviving at 1 year. In addition, late and evolving eye lesions can be detected later in patients without apparent initial ocular involvement.

Given the high prevalence, possible late onset, and possible severity of sequelae, expert recommendations [25] are:

- to inform patients and their physicians of the risks;
- to schedule follow-up examinations and referral to organ specialists as needed.

Only ocular sequelae were the topic of therapeutic studies, including a few RCTs [20–23]. Unfortunately, most patients



included in these RCTs had ocular lesions of other causes and likely different mechanisms, allowing no conclusion specifically related to SJS/TEN.

### Possible benefits

We found two open trials of gas-permeable scleral contact lenses in patients with ocular surface lesions resulting from SJS/TEN that suggested an important improvement of pain, photophobia, vision, and quality of life [69,70].

### Comment

The high prevalence of long-lasting sequelae means that SJS/TEN should be considered not only an acute life-threatening event but also a chronic debilitating disease. Efforts should be directed to understanding the mechanisms of sequelae and designing and evaluating interventions aimed at their prevention and management.

### What happens in cases of rechallenge with the causative drug or a related drug?

We found no evidence on risk of reuse of culprit drug and on the possibility of desensitization in patients with TEN.

Large prospective cohorts of patients (SCAR, EuroSCAR, RegiSCAR) included a few patients who had a history of prior SJS or TEN always attributed to the same medication that was considered responsible for the recurrence. Even though an old series of oral reintroduction tests in TEN (10 cases) and SJS (eight cases) resulted in recurrence in only two cases [71], the risk for life is so high that avoiding the culprit drug and compounds closely related chemically is recommended [25].

There is no evidence to suggest that patients who have had SJS/TEN should avoid all “strongly associated” medications when not related to the one that induced their disease [25].

Some data are available for desensitization in benign cutaneous adverse drug reactions using escalating doses. Using such a protocol in a patient with a history of SJS or TEN could be considered acceptable only in the case of vital need and absence of alternative medication.

### Interventions

#### Found to be beneficial

- HLA testing prior to administration of “strongly associated” medications has a preventative role, but only for a few drugs and selected population groups.

#### Likely to be beneficial

- Avoiding prescription of “strongly associated” medications that lack evidence of usefulness.
- Prompt withdrawal of potentially causative drugs.
- Prompt referral to highly specialized center.
- Symptomatic treatments.

#### Unknown effectiveness

- Systemic corticosteroids, IVIGs, plasmapheresis, cyclosporine A.

#### Harmful

- Thalidomide.

### Key points

#### Prevention

- We found evidence that excluding patients harboring a specific HLA allele decreased the risk of carbamazepine-related SJS/TEN in Han Chinese. That exclusion probably applies also to other populations in South East Asia.
- We found evidence that some “strongly associated” medications are too often prescribed without evidence-based rationale (e.g., anticonvulsants for prevention of seizure in patients with brain tumors or allopurinol for asymptomatic hyperuricemia).

#### Specific treatments

- We found insufficient evidence about effective “specific” treatments.
- We found only one placebo-controlled RCT, which reported a higher mortality with thalidomide regimen.
- We found three systematic reviews and one large cohort study suggesting no benefit from using systemic corticosteroids or IVIGs in addition to symptomatic care.
- We found no good evidence on the effects of any other “specific treatment.”

#### Supportive care

- We found no evidence on the value of supportive care applying directly to SJS/TEN, but expert recommendations that most measures demonstrated to be beneficial in severe burns are likely useful in SJS/TEN.

#### Value of tests

- We found no evidence.

#### Drug reintroduction

- We found insufficient evidence.

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# Polymorphic light eruption

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## Introduction

The condition polymorphic light eruption (PLE), also known as polymorphous light eruption, is one of the group of idiopathic photosensitivity disorders that also includes hydroa vacciniforme, chronic actinic dermatitis (photosensitivity dermatitis and actinic reticuloid syndrome), idiopathic solar urticaria, actinic prurigo, and juvenile springtime eruption. Although the cause of each of these conditions remains unknown, there are suggestions that the mechanism for some, including PLE, may be autoimmune. Here, I discuss some aspects of PLE (Figure 69.1), by far the commonest of these conditions, on which there is the largest volume of published literature. Where appropriate – for example, when discussing differential diagnosis – I mention other photodermatoses. Other photodermatoses, such as cutaneous porphyrias, DNA-repair disorders (such as xeroderma pigmentosa), and drug-induced photosensitivity, will be dealt with in future editions of the book and on the accompanying website.

## Background

### Definition

PLE is a recurrent abnormal reaction to sunlight – or artificial ultraviolet (UV) radiation – that occurs after a delay following exposure and heals without scarring [1–3].

### Prevalence

Questionnaire surveys have found that 10–21% of selected northern European and North American populations are affected [4–6]. PLE is diagnosed less frequently closer to the equator [7–9].

### Etiology

A commonly postulated mechanism is that PLE might be an autoimmune disorder in which there is an abnormal delayed hypersensitivity to an endogenous molecule rendered antigenic by UV exposure [10].

## Prognosis

Spontaneous resolution can occur, but is probably infrequent amongst those affected severely enough to be assessed in hospital [11].

## Diagnostic tests

The diagnosis is usually made on the basis of the clinical history. The following investigations are sometimes indicated:

- *Lupus serology*, when cutaneous lupus erythematosus is considered in the differential diagnosis; particularly if treatment with prophylactic phototherapy is being considered, antinuclear antibody and anti-Ro and La antibodies should be requested [12].
- *Histopathology*, when a superficial and deep, perivascular, dermal inflammatory infiltrate is seen. Histopathology and direct immunofluorescence can help differentiate PLE and lupus erythematosus [13,14].
- *Phototesting*. Monochromator phototesting is usually normal in PLE, but can be useful in excluding solar urticaria or chronic actinic dermatitis if these are considered possible alternative, or concomitant, diagnoses. Repeated irradiation provocation testing to 4 cm × 4 cm or larger areas is positive in a proportion of patients (<50% in some series), but can be helpful in cases of diagnostic uncertainty.
- *Patch testing and photopatch testing to sunscreens*. These are useful when sunscreen photoallergy or contact allergy is suspected as a coexistent diagnosis [15–18].
- *Porphyria plasma spectrofluorometry*. Cutaneous porphyrias occasionally feature as differential diagnoses, and can be excluded if this simple test is negative.
- *HLA class II typing* can help distinguish actinic prurigo (see later) [19,20].

## Aims of treatment

Treatments can be divided into prophylactic or suppressive. Prophylactic measures include sunlight avoidance and “desensitization” prophylactic phototherapy. Sunlight avoidance measures





Figure 69.1 A typical papular polymorphic light eruption.

include advice on behavior (for example, avoiding outdoor exposure between 10 a.m. and 3 p.m.), clothing (long sleeves and hat), topical broad-spectrum sunscreens, and environmental measures (such as applying UV-absorbing “museum film” to house and car windows for those severely sensitive to UV wavelengths). The aim of these measures is to reduce the frequency of and severity of the eruption.

The aim of prophylactic phototherapy is to increase the duration of sunlight exposure required to elicit PLE, and so improve the quality of life for those severely affected patients who cannot carry out normal activities (for example, putting out washing during daytime) because very limited sunlight exposure triggers the eruption. Suppressive treatment should alleviate symptoms (particularly itch), and speed the resolution of PLE when it occurs.

### Relevant outcomes

For prophylactic treatments, important outcomes are number of episodes of PLE (and their severity) and quality of life. For symptomatic suppressive therapies, the main outcomes are symptom severity (primarily itch) and the speed of resolution of the eruption.

### Methods of search

Studies were identified using the Medline (1966 to January 2006) and Embase (1988 to January 2006) databases, with search terms including “polymorphic/polymorphous light eruption AND (treatment OR prognosis).” Abstracts were read to determine which were likely to be relevant.

## Questions

### What is the prognosis for resolution of polymorphic light eruption for a severely affected patient living in a temperate country?

Follow-up of 94 Finnish patients (by questionnaire, supplemented by repeat clinical assessments of a subgroup) up to a mean of 32 years after onset found that 24% (95% confidence interval [CI], 16–34%) experienced resolution of their PLE and that 51% (95% CI, 41–62%) had milder PLE [11]. A recent report suggested that those with negative provocation tests may be more likely to proceed to remission than those with positive provocation tests [21].

## Comments

We have very limited information on the prognosis of PLE, and this one well-conducted follow-up study [11] involved a selected group of patients – those assessed in a hospital department and willing to attend for review. Our experience in Dundee (based on another severely affected patient group) is that a substantial proportion of those with PLE severe enough to require repeated yearly prophylactic phototherapy do, after several years, experience resolution, or marked improvement, so that they can then stop attending for treatment [22]. We do not know whether this is spontaneous resolution or whether it is a result of repeated phototherapy courses.

### Implications for practice

We can advise patients that spontaneous resolution is possible, but cannot reliably indicate how likely it is to occur. We still do not know whether repeated yearly courses of prophylactic phototherapy influence the long-term prognosis.

### Which form of prophylactic phototherapy – psoralen-ultraviolet A photochemotherapy or ultraviolet B monotherapy – should be prescribed for severely affected patients?

#### Efficacy

A randomized, patient-masked, controlled trial [23] including 25 adults found that narrowband (TL-01) ultraviolet B (UVB) was as effective as psoralen-ultraviolet A (PUVA) in preventing episodes of PLE following a treatment course, and that it was possibly more effective in reducing posttreatment subjective PLE severity scores. PUVA is more effective than broadband UVB [24].

#### Drawbacks

Both TL-01 UVB and PUVA produced PLE during the treatment course in about half of those treated [23]. High cumulative PUVA exposures administered to psoriasis patients increase the risk of later development of skin cancers, particularly squamous cell carcinomas [25]. Although the risks with UVB have not been well defined, it is probable that high cumulative UVB exposure will also result in some increased skin cancer risk (but less than with PUVA).

## Comments

The analysis of each of these studies comparing PUVA with UVB (narrowband and broadband) as prophylactic therapies for PLE took into account natural UV exposure measured with polysulfone badges after the treatment courses. Even with randomization (methods for which were not defined in either paper), differences in subsequent sunlight seeking or avoidance behavior in the groups compared could have influenced the results. Insufficient raw data were presented to allow retrospective calculations of the power of either study. Nevertheless, it can be safely concluded that PUVA is not much more effective than TL-01 UVB, and may even be less effective.

### Implications for practice

TL-01 UVB is the prophylactic phototherapy of choice for patients severely affected by PLE. When it fails to provide useful benefit, or when repeated episodes of PLE are provoked during therapy, PUVA can be considered.

## What are the effects of corticosteroids for mildly affected patients who develop polymorphic light eruption while on holiday?

### Efficacy

A randomized controlled trial of prednisolone 25 mg/day in a presumably mildly affected group (only 10 of 21 patients needed to take the study drug while on vacation) showed that it had an effect. PLE resolved more quickly (by a mean of 3.6 days; 95% CI, 0.6–6.1 days) with prednisolone than with placebo, despite the fact that for this study the patients were encouraged to continue sun exposure after they developed PLE [26].

It is unclear whether moderately potent or potent topical steroids help to suppress established PLE, but potent topical steroids may be of value prophylactically if applied immediately after exposure [27].

### Drawbacks

One of 10 patients who took a short course of oral prednisolone for PLE experienced “mild gastrointestinal disturbance and slight depression of mood” [26].

### Comments

For most patients with mild PLE, it is doubtful whether the small improvement produced by systemic prednisolone is sufficient to outweigh concerns about side effects. We do not know whether a potent topical steroid is of benefit for established PLE, but as systemic steroids have an effect it is possible that, at least for some patients, this may be beneficial.

### Implications for practice

Corticosteroids can have a small to modest effect on established PLE. While there is a lack of evidence that topical steroids have a similar effect, it may be appropriate to prescribe a potent topical steroid to use if PLE develops for patients whose problem is mild and confined to episodes induced by holiday sunlight. For some who are infrequently affected, application of a potent topical steroid each day before exposure may prove a useful approach.

## Can human leukocyte antigen class II typing distinguish polymorphic light eruption from actinic prurigo?

Actinic prurigo is strongly associated with HLA-DR4, and particularly HLA-DRB1\*0407 in the UK [19,20] and Mexico [28].

### Comments

PLE is distinguished from actinic prurigo on the basis of history and clinical features. The finding of a strong human leukocyte antigen (HLA) association with actinic prurigo, but not PLE, strengthened the evidence that these are distinct diseases. A study to determine the value of HLA class II typing as a diagnostic test in cases of clinical uncertainty about the diagnosis has not been performed, but such testing could be helpful.

### Implications for practice

In cases in which the diagnosis is in doubt, a negative HLA-DR4 test makes actinic prurigo less likely than PLE, while a positive HLA-DR4 is of limited value, as this antigen is common (about 25%) in most populations. A positive HLA-DRB1\*0407 test (rare in most populations) may help to rule in a diagnosis of actinic

prurigo (and exclude PLE), whereas a negative test result (found in almost 40% of UK cases of actinic prurigo) is of limited value.

### Key points

- PLE can improve over the years. This improvement may be spontaneous or partly due to repeated prophylactic phototherapy.
- Narrowband UVB and PUVA are similarly effective in preventing episodes of PLE.
- Oral prednisolone has a small or modest beneficial effect in PLE.
- Is not clear whether topical corticosteroids are of help in suppression of established PLE.
- HLA typing may occasionally be helpful in classifying a photodermatosis with features of both PLE and actinic prurigo.

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# Infantile hemangiomas

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## Background

### Definition

Infantile hemangiomas (IHs) are benign endothelial tumors that characteristically have an initial rapid proliferative phase and a later, slower involutional phase (Figure 70.1). An IH may be composed of a superficial component with a bright red color and a blue-tinged color signifying the deeper component. They may be cutaneous or extracutaneous, although extracutaneous IHs will not be discussed in this chapter.

### Incidence/prevalence

The estimated incidence in children is 1.1–5% at birth [1–3], rising to 10% at 1 year of age [4,5]. The true incidence is not known, as they are often not present at birth, and the few prospective studies that have been conducted have methodological flaws. They were undertaken prior to the accurate classification of vascular birthmarks. IHs are three times more common in females and less common in some ethnic groups [6,7]. They are more common in premature infants and those with low birth weight; the incidence has been reported to be as high as 20% in premature infants with a birth weight of less than 1000 g [8,9].

### Etiology

The pathogenesis has yet to be fully elucidated, but clues are evident from a better understanding of vascular biology. Hemangiomas are proliferative lesions composed of endothelial cells (ECs), supporting pericytes, myeloid cells, and other cells, such as fibroblasts and mast cells [10,11]. Examination of isolated hemangioma ECs and whole tumors suggests that hemangiomas arise from uncontrolled clonal expansion of ECs [12]. The processes leading to the development of new blood vessels is complex and poorly understood. In proliferating hemangiomas, there is increased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth

factor [13,14]. Other growth factors, such as insulin growth factor and integrins relevant to angiogenesis,  $\alpha 5\beta 3$  and  $\alpha 5\beta 1$ , are expressed in the proliferative phase of hemangiomas [11,15]. In involuting hemangiomas, VEGF expression is reduced with a concomitant rise in the expression of apoptosis-associated proteins [16].

It is now apparent that ECs from IHs can be distinguished from other vascular tumors and malformations by surface markers such as GLUT-1, an erythrocyte-type glucose transporter protein, Lewis Y antigen, Fc gamma receptor II, and merosin [17,18]. These markers are also expressed at high levels on placental vasculature, leading workers to postulate hemangiomas may be a result of embolization of placental endothelial cells. Placental embolization has been shown not to be the case by using highly sensitive molecular genetic techniques which showed no evidence of maternal-fetal chimerism [19,20]. More recent work has focused on hypoxia as the underlying stimulus to development as a result of investigating the mechanism of action of propranolol in IHs (see later).

### Prognosis

The natural progression of hemangiomas can be divided into a rapid proliferative phase and a much slower involution phase (an artificial division, but clinically useful). The mean period of proliferation is 5 months (International Society for the Study of Vascular Anomalies data 2006), with an estimated 80% of growth of superficial IH achieved by 3 months [21]. Deeper lesions often proliferate up to 12 months of age. Involution may begin in the first year and may occur in one part, whilst other parts are still proliferating. The plaques often break up into smaller islands, and involution can continue for up to 10 years. The seminal studies of the natural history of untreated IH, from which much of current-day prognosis is based, showed that involution is completed in 50% by 5 years, 70% by 7 years, and 90% by 9 years [22,23]. There is a wide variation in what remains after involution, ranging from complete disappearance, telangiectasia, or more commonly a fibro-fatty residuum.





**Figure 70.1** In this 4-month-old child, a red mark was first noted on the right cheek at the age of 3 days. The mark grew rapidly during the first few months, despite early laser treatment. The mixed superficial and deep hemangioma involved the infraorbital area and ulcerated at the age of 3 months. As it was growing rapidly close to the eye and was likely to leave residual deformity, it was treated with a course of oral prednisolone, with stabilization of growth. Ophthalmic assessments were normal. The ulceration healed with wound care. At the age of 4 years, there was a residual fibroadipose structure, which was surgically corrected.

Sites such as the lips, nose, and cheeks leave cosmetically more disfiguring residua. IHs with ulceration tend to leave white or yellow scars.

### Treatment

There has been a major Cochrane review of interventions for infantile hemangiomas, and readers are directed to this very useful resource [24]. A significant but very important minority of hemangiomas may cause functional problems or even permanent cosmetic disfigurement. The decision to treat is obvious when IHs are potentially life threatening, or function threatening, as in those hemangiomas with heart failure, ocular compromise, or respiratory distress.

The site and size of the hemangioma will dictate the need for treatment. Sites such as the lips, nose, or ears are more likely to lead to permanent anatomical distortion and scarring [25,26]. The scarring from large plaque-like segmental hemangiomas on the face is potentially more serious than a similar lesion on the trunk.

The point in evolution of the hemangioma will also be relevant to management, and is closely linked with the age of the child. Hemangiomas of similar appearance may be in involution in an older child whilst in the growth phase in a child at 4 months old. The decision to treat surgically, for example, should normally be taken after the hemangioma has completed its growth phase.

The developmental stage of the child must also be taken into account, as children start becoming body aware at 2–3 years of age, but realization of a problem leading to stigmatization rarely occurs before 4–5 years of age. The decision to continue a wait-and-see approach must be balanced against the emotional consequences of this decision [27]. All children must be treated on an individual basis, but the parents should have information to help guide their decision. The information may take the form of serial photographs, examples of previous cases with before and after photographs, and a full discussion of the risks and benefits of any treatment modality. The following summarizes the indications for treatment

- life-threatening IHs (e.g., airway obstruction);
  - function threatening (such as visual or hearing compromise);
  - complications (e.g., ulceration);
  - large/segmental IHs likely to result in poor cosmetic outcome.
- The aims of treatment are resolution of the hemangioma without scarring, to reduce psychosocial morbidity, and prevent complications.

### Relevant outcomes

- Objective measures of resolution, such as redness, surface area, height.
- Residual skin changes, such as skin hypopigmentation, atrophy, fibro-fatty tissue, and telangiectasia.

### Methods of research

The Cochrane Library, Medline, and Pubmed until September 2012 were searched for terms including hemangiomas, propranolol, corticosteroids, and treatment. Abstracts were read and all potentially relevant studies were obtained in hard copy.

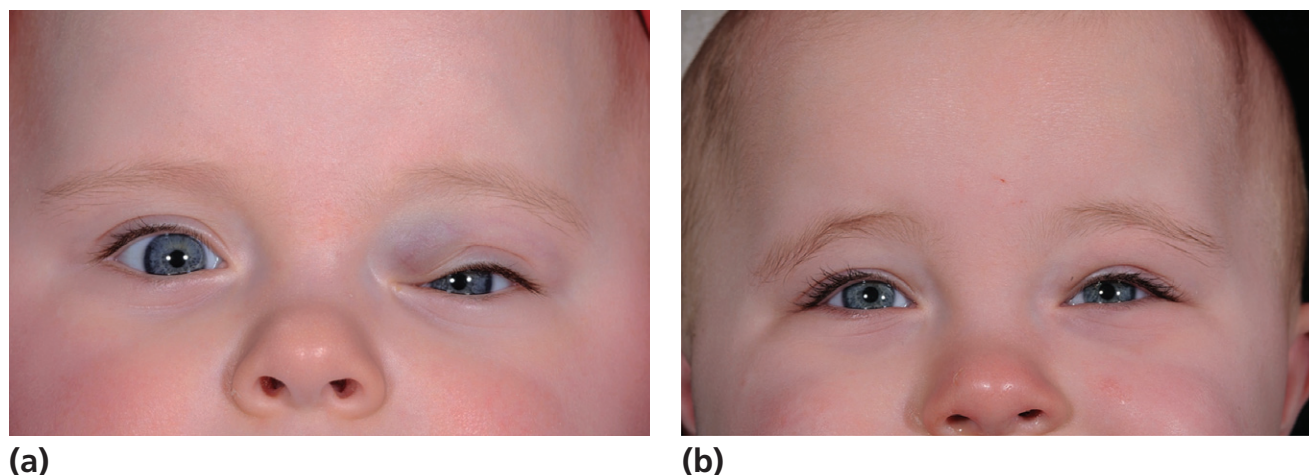
## Question

### Should propranolol be considered as first-line treatment for all problematic hemangiomas?

In a previous edition of this book it was reported that oral corticosteroids were effective in several case series, although no randomized controlled trials (RCTs) were available. It would be difficult to justify an RCT with a control observation arm in children with a complicated IH. Oral corticosteroids have until now been the gold standard for treatment of complicated IH. Since the first report of the unexpected discovery of the therapeutic benefit of propranolol used to treat heart failure in an infant with a facial hemangioma in 2008 [28], the vascular anomaly literature has mushroomed with reports of experience mainly in case series [29] (see Figure 70.2). However, as with any novel therapy (albeit an “old” drug), there should be a solid evidence base before it becomes accepted as the first-line therapy. This author is aware from experience that many physicians are already using it as first line because of its dramatic response.

Propranolol works by different mechanisms, including vasoconstriction, inhibition of angiogenesis, and induction of apoptosis [30]. Furthermore, it is believed that propranolol specifically induces regression of hemangioma endothelial cells through hypoxia-inducible factor-1 $\alpha$  (HIF)-mediated inhibition of the VEGF-A angiogenic axis [31].

The only published RCT of propranolol in IH compared propranolol 2 mg/kg per day with placebo for 6 months [32]. Forty children aged between 9 weeks and 5 years with facial IHs that were



**Figure 70.2** (a) Prior to treatment of upper eyelid hemangioma; (b) 5 months posttreatment with propranolol 2 mg/kg per day.

likely to result in cosmetic disfigurement or impair function were split into the two arms. The outcome measures were hemispheric volume, redness, and elevation scores, with serial photography as assessed by blinded observers. Some of the patients had not previously responded to oral corticosteroids. The results were analyzed on an intention-to-treat basis. Significant reductions in all parameters were seen from 1 month onwards. The IHs were clinically softer and less tense, although the dramatic change in the first 4 weeks had plateaued by 6 months. Furthermore, there were no reported serious side effects of bradycardia, hypotension, or hypoglycemia. The most common reported adverse effects were bronchiolitis, upper respiratory tract infection, and sleep disturbance.

### Drawbacks

This is data from small numbers of children, and the sample of patients used was quite mixed in age with very few early in their evolution and others who were quite advanced in their involution. The measurements were blinded, but volume measurements are notoriously prone to error. More objective measures are required, although in clinical practice serial photographs remain the most common method of assessment.

### Comment

There are many unanswered questions that need to be addressed with long-term prospective RCTs. The following shows the trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) and <http://anzctr.org.au/TrialSearch.aspx>) being undertaken to resolve these issues:

- Does the use of propranolol bring forward the natural end point of evolution?
- Are there any long-term side effects?
  - **NCT01211080** Uncontrolled prospective observational study looking at cardiopulmonary and metabolic side effects of propranolol 2 mg/kg per day at 8 months.
- What is the best dose regime and for how long should it be given?
  - **NCT01056341** RCT of oral propranolol (1 or 3 mg/kg per day for 3 or 6 months) versus placebo in proliferating hemangiomas requiring systemic treatment.

- Should the extension of indications include noncomplicated IHs including small lesions?

- **NCT00744185** RCT of oral propranolol (3 mg/kg per day increasing to 4 mg/kg per day) for 30 days versus placebo in capillary hemangiomas. This trial is for IHs that would not normally be considered for treatment. Unfortunately, this study was terminated owing to recruitment difficulties.
- **NCT01512173** Double-blind placebo RCT comparing propranolol gel for 12 weeks with placebo.

- How should patients be selected for treatment?
- Is it better for those IHs in the expansion phase or should it be used at all stages of their natural history?

A case series showed that, in 37 patients in whom it was documented regression had ceased or greater than the age of 12 months, there was proven efficacy by comparing digital photographs [33]. The authors of this study stated that propranolol should be considered as first line for post-proliferative IH. The efficacy in the only completed RCT noted above was not 100%. Published case series report efficacy between 97 and 100%, although this is not always excellent/complete response [34–38]. This range is important in clinical practice because not all children with IH will respond to propranolol. The nonresponder rates can be up to 3% [34–38]. There need to be options for these patients.

- Is propranolol more effective than prednisolone?

As oral corticosteroids have been the previous first-line treatment, this modality should not be forgotten. A retrospective study comparing propranolol 2 mg/kg/day (for 8 months) with prednisone 4 mg/kg/day (5 months) showed that propranolol was more effective, cost effective and resulted in fewer surgical interventions and adverse effects [39].

- **NCT00967226** RCT of oral propranolol (2 mg/kg per day) versus oral prednisolone (2 mg/kg per day) for 4–6 months in symptomatic hemangiomas. This trial is ongoing.
- **NCT01072045** RCT of oral propranolol (2 mg/kg per day) versus oral prednisolone (2 mg/kg per day) for 60 days in proliferative or involuting hemangiomas.

There is marked variation in the pretreatment assessment of children, with protocols varying from inpatient assessment with pulse,

blood pressure (BP), echocardiogram, electrocardiogram (ECG) and blood glucose, to an outpatient setting with an ECG, BP, and glucose. The situation is constantly evolving as more experience is gained and monitoring is less stringent. When propranolol treatment for IHs is discussed with cardiologists, they are surprised by the level of assessment in patients with such low doses of propranolol compared with the doses used in heart failure and other cardiac diagnoses.

There are trials which are ongoing looking at other similar agents; for example, atenolol, nadolol, and timolol gel 0.5%. The latter is being studied very closely as it may bypass the need for pretreatment assessment and be easier for routine clinical use.

- NCT01010308 Nonrandomized intervention trial of nadolol 0.5–2 mg/kg per day for 6 months in 10 infants to explore the efficacy and safety of nadolol in IH.
- ACTRN12610001069044 RCT of topical timolol maleate gel 0.5%, one drop, versus emollient eye-drop placebo applied twice daily for 24 weeks (<http://anzctr.org.au/TrialSearch.aspx>).
- NCT01147601 RCT of topical 0.5% timolol for 6 months versus placebo, two or three drops to cover small (less than 3 cm) hemangiomas, twice daily.

The answer to the original question is that propranolol should be considered as first-line treatment for complicated IHs (except in patients with syndromic hemangiomas, such as posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, eye abnormalities, and sternal abnormalities or ventral developmental defects (PHACES) syndrome [40], where there is potentially risk of cerebral hypoperfusion), but with several caveats. The dearth of long-term prospective data makes it impossible to say whether propranolol is better than other treatments in the long term, and larger multicenter studies are required. The safety profile is promising, especially compared with oral corticosteroids, but data collection should be continued over a longer period. The use of propranolol cannot be advocated in small asymptomatic lesions without more RCT evidence.

### Key points: infantile hemangiomas

- IHs are common vascular tumors with clinical heterogeneity and generally do not require intervention.
- For the small but significant complicated IHs that require intervention, steroids were considered first-line therapy. It has now been superseded by oral propranolol. There are two ongoing RCTs comparing oral prednisolone with propranolol.
- Propranolol is effective in the treatment of IHs, although there is only one small published prospective RCT demonstrating efficacy.
- There are numerous RCTs underway to confirm the efficacy, dose regime for oral propranolol and other trials of topical beta blockers.
- No long-term safety data are available, and there is a lack of evidence that the natural history of long-term involution is altered by propranolol treatment.
- There is no agreed screening or treatment protocol for the use of propranolol in IH.

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## Background

Pruritus is defined as an unpleasant sensation that leads to a desire to scratch. It is the predominant symptom of skin diseases. All human beings experience this sensation in the course of their lifetime; therefore, it is important to make a distinction between acute itch, which is of a limited period of time ranging from seconds to <6 weeks, and chronic pruritus, which lasts for a period of >6 weeks [1]. The focus of this chapter is chronic pruritus. The consequences of pruritus range from trivial discomfort to excruciating distress. Chronic pruritus may cause substantial impairment of the quality of life and sleep of patients, which is similar to chronic pain [2–4].

Occasionally, heavy excoriations caused by intense pruritus can lead to serious secondary skin infection. Most skin diseases itch, especially if they have an inflammatory or epidermal component, and these diseases are discussed in the relevant chapters elsewhere in this book.

## Definitions

With a view to facilitating investigation and treatment, pruritus has been classified [5,6] into four categories, which are not mutually exclusive:

- pruritoceptive – itch generated in the skin due to skin disease;
- neuropathic – due to lesion(s) in the central or peripheral nervous system;
- neurogenic – caused by presumed circulating pruritogens, without evident disease of the nervous system;
- psychogenic – including delusional and affective disorder.

According to the International Forum on the Study of Itch (IFSI), pruritus has been classified into categories [1] that first distinguishes three clinical groups of patients as follows:

- Group I – pruritus on diseased (inflamed) skin;
- Group II – pruritus on nondiseased (noninflamed) skin;
- Group III – pruritus presenting with severe chronic secondary scratch lesions.

The first group includes underlying dermatological diseases, while the second and third groups include patients with systemic diseases, neuropathic itch, and psychiatric disorders, as well as diseases of pregnancy and drug-induced pruritus. The IFSI classification also contains an etiological classification of chronic pruritus: I, dermatological; II, systemic; III, neurological; IV, psychogenic/psychosomatic; V, mixed; and VI, other (undetermined origin) [1]. This new classification considers that some patients have more than one cause accounting for pruritus (category “mixed”) while in others no underlying disease can be identified (category “others”) [7].

Measurement of pruritus remains a challenge. In recent years, tools to assess its intensity using a visual analogue scale were validated [7,8]. Pruritus is subjective and, therefore, difficult to quantify, resort usually being made to a digital visual analogue scale [7,9]. Pruritus has also been measured indirectly by quantification of scratching or rubbing – for example, by using limb movement meters. However, the specificity of this method in distinguishing between restlessness and pruritus is unclear.

In summary, several instruments for the assessment of itch exist. However, it is clear that the use of a single measure does not insure an adequate and comprehensive assessment of itch [8,10].

## Incidence and prevalence

While it is often stated that pruritus is the most frequent symptom in dermatology and that it may also occur in other diseases (e.g., systemic, neurological), there are only a few studies about the prevalence and incidence of pruritus. In particular, chronic itch in the community has to be distinguished from chronic itch in specific populations, such as children and elderly people, and chronic itch in specific diseases [11]. One of the first population-based studies of pruritus was the so-called “Lambeth study” [12]. The point prevalence of pruritus and similar diseases such as prurigo and similar conditions was 8.2% in an urban adult population [12]. A population-based French study reported a 2-year prevalence of

14.4%, but there was no definition given of how chronic pruritus was defined [13]. A population-based study in Oslo, Norway, in 2000–2001 assessed among many other variables self-reported skin complaints. It was found that 8.4% of the survey individuals ( $n = 18747$ ) aged 30–76 had suffered from acute pruritus during the past 2 weeks [14]. In a study among employees attending an early skin cancer detection program, the point prevalence of chronic pruritus (>6 weeks) was 16.7% [15]. The Heidelberg pruritus prevalence study aimed at assessing the prevalence of pruritus (>6 weeks) in two urban populations and one world population. A previously validated questionnaire developed for the assessment of the prevalence and characteristics of chronic pruritus in the general population was used [16]. The point prevalence was estimated to be 13.5%, the 12-month prevalence 16.4%, and the lifetime prevalence 22% [16]. Women were affected more often than men, but a significant gender difference was only found for lifetime prevalence. Individuals with a non-German background reported significantly more chronic pruritus than Germans [16].

The findings of studies, especially in epidemiology, on pruritus are often difficult to compare or interpret owing to the fact that the parameters are not operationalized in a consistent manner and are not clearly defined. Besides, the symptom of “pruritus” often receives only minor attention in nondermatological specialties and is, therefore, often not considered in clinical studies. Pruritus is said to occur frequently in systemic diseases, but there is no epidemiological data on the frequency of pruritus in systemic diseases in general, and data for specific systemic diseases refer mainly to uremic pruritus [11]. Considering the most common skin diseases, pruritus is a defining feature of atopic eczema and daily pruritus is described in 84–91% of patients with atopic eczema [17,18]. According to a patient survey, atopic eczema patients were more likely to experience current pruritus and report a higher pruritus intensity compared with psoriasis patients [19]. Sixty-eight percent of chronic idiopathic urticaria patients were found to suffer from chronic pruritus which occurred daily [20].

### Prognosis

If a cause can be identified and dealt with (e.g., identifying the underlying dermatosis, relief of biliary tract obstruction in pruritus of cholestasis), the itch should remit. However, even when a cause has been identified (e.g., pruritus of chronic renal failure (CRF)), the itch may persist unabated despite best efforts. However, owing to increased research efforts, the number of therapeutic treatments has increased [21].

### Diagnosis

A careful history and examination are crucial. The quality, diurnal or nocturnal periodicity, and duration are very important. Itch with burning sensation and limited localization could be a form of neuropathic itch. A simple question, such as whether pruritus occurs in other family members, can indicate the possibility of scabies and avoid unnecessary investigation. A positive review of symptoms such as night sweats, loss of weight, and tremor may point to a systemic cause. Itching often occurs in brief bouts (e.g., at bedtime), and this information allows appropriate fine-tuning of treatment. Questionnaires such as the Eppendorf itch questionnaire [6] have proven useful in evaluating the intensity of itch and the resulting handicap, but there is no single and definite questionnaire fulfilling all needs [3,8,18]. As there is no definite itch questionnaire, it is obvious that additional tools are needed to better assess the different dimensions of chronic pruritus and better tailor management [8].

Examination for scabies burrows and for symptomatic dermographism (firm stroking of skin causes wheal, flare, and itch) should be done routinely. Care should be taken not to confuse induced secondary eczematous changes – as a consequence of rubbing or scratching due to a systemic cause of itch – with a pruritoceptive itch caused by a primary skin disease.

### Aims of treatment

The aim of treatment is to alleviate the itching, the distress it causes to the patient, and the secondary changes wrought in the skin by scratching. The European guideline on chronic itch has been published [21], and this addresses all medical disciplines that work with patients suffering from chronic itch.

### Relevant outcomes

In practice, total abolition of itching in the chronically pruritic patient is rarely achieved, and its partial amelioration is a more or less acceptable compromise outcome. For example, it is often possible to relieve itching to the extent that it does not interfere significantly with the patient's daily activities or cause excessive sleep disturbance at night.

### Methods of search

The following key words were used in a literature search: itch, pruritus, prurigo, scratch, excoriation.

We reviewed Pubmed, Medline, Embase, and the Cochrane Library and conference proceedings on pruritus. In addition, a manual search of the major German dermatology journals was carried out.

## Pruritus of chronic renal failure

### Definition

Pruritus of CRF is multifactorial in causation and variable in its clinical presentation, and therefore eludes precise definition. It is often unremitting, sometimes episodic. In the majority of patients it is generalized and symmetric in distribution, but could be localized – often to the shunt arm in dialysis patients. It is frequently associated with secondary skin complications, such as prurigo nodules and lichenified plaques.

### Incidence

The incidence of pruritus in CRF patients on dialysis has fallen in recent years from 70% 25 years ago to an estimated prevalence range between 22 and 60% [22–25]. In the largest epidemiological study to date, the international Dialysis Outcomes and Practice Patterns Study (DOPPS) determined that the prevalence of moderate to severe pruritus among more than 18 000 dialysis patients was 42%. No association was found between the presence of pruritus and gender, age, ethnicity, level of education, duration of end-stage renal disease, nature of underlying renal disease, or type of hemodialysis. Acute renal failure does not cause itching. It is extremely rare in children. It is more common in patients receiving hemodialysis than in those receiving continuous ambulatory peritoneal dialysis [26]. In patients on dialysis, it is an independent risk factor for mortality [25].

### Etiology

The cause of pruritus in CRF is unknown. It is thought to be a multifactorial disorder. Possible mechanisms include peripheral

C fiber neuropathy/abnormal innervation, mu opioid-kappa opioid imbalance, immune system derangement with a predominant TH1 proinflammatory response, and skin barrier abnormalities [27–30].

Recent studies, including the large DOPPS study, have demonstrated that higher serum calcium (albumin corrected) as well as phosphorus and calcium phosphorus product above  $>80 \text{ mg}^2/\text{dL}^2$  are all associated with itch intensity [24].

Xerosis is very common in CRF patients and probably contributes to itching in some patients, but it is not the major cause of itch [31].

## Prognosis

There are no systematic studies of the natural history of pruritus of CRF, but it is widely perceived to be unremitting and poorly responsive to treatment.

## Treatment aims

The primary object of treatment is to remove or mitigate any identifiable cause and abolish or at least ameliorate the itching. Patients with pruritus of CRF are frequently depressed and despairing of any effective remedy, so any treatment strategy needs to take depression into account, including counseling and the use of antidepressants. The only reliably effective treatment for pruritus of CRF is a kidney transplant.

## Outcomes

Reduction or abolition of pruritus should lead to resolution of the secondary manifestations of itching, including excoriation, eczematization, and secondary infection and relief of xerosis. Successful treatment should be reflected in an improvement in the patient's sense of well-being and quality of life.

## What are the guiding principles in choosing treatments for pruritus of chronic renal failure?

### General measures

Treatment of xerosis by emollients brings about some symptomatic relief. A double-blind trial using glycerol cream and paraffin showed a 75% reduction in pruritus and improvement in xerosis [32]. Another emollient containing gamma linoleic acid, an essential fatty acid, reduced itch significantly in a randomized, double-blind study of 22 patients [33].

A topical emollient containing palmitoylethanolamide (PEA), an endogenous fatty acid amide and a cannabinoid agonist, completely eliminated CRF pruritus in 38% of patients in an open-label 3-week trial [34]. Owing to the lack of controls and a significant placebo effect, further double-blind studies are warranted to examine the utility of PEA-containing emollients in the treatment of CRF pruritus.

Other topicals include topical anesthetics. In a double-blind study, pramoxine, a topical analgesic, relieved chronic kidney disease (CKD) pruritus in hemodialysis (HD) patients. It has no reported systemic side effects and is available as an over-the-counter agent [35].

In a crossover double-blind study, 19 out of 22 HD patients with moderate to severe pruritus treated with topical capsaicin 0.025% reported some relief and seven patients had a complete remission [36].

Topical tacrolimus 0.03%, a topical calcineurin inhibitor, reduced CRF pruritus in a case series and an open-label study [37]. However,

a randomized double-blind vehicle-controlled trial in 22 HD patients with moderate to severe pruritus revealed that the vehicle was similarly effective [38]. A recent study using pimecrolimus, a topical immunomodulating drug, similar to tacrolimus, was not effective either [39].

Secondary infection and eczematization can usually be controlled by topical treatment with a combination of antibiotics and corticosteroids. The intensity of pruritus correlates with skin temperature, so a cool environment, tepid showering, and wearing of light, loose-fitting clothes are beneficial.

### Systemic therapies

Although no results are available from controlled studies, oral antihistamines are of little or no value in the management of pruritus of renal failure.

Opioid  $\mu$ -receptor antagonists, which have been found to be effective in pruritus of cholestasis (see later), have also been advocated in the treatment of pruritus of renal failure. However, the published results have been conflicting. A randomized, placebo-controlled crossover study by Peer *et al.* [40] showed that the oral  $\mu$ -receptor antagonist naltrexone (50 mg/day) was effective, with all of 15 patients responding with reduced itching. However, a subsequent placebo-controlled double-blind crossover study that included 23 patients taking oral naltrexone 50 mg daily, with a visual analogue scale and a detailed score to measure pruritus intensity, showed no difference in comparison with placebo [41]. Nalfurafine hydrochloride is a kappa opioid agonist that mitigates the effect of mu opioids. In two large, randomized double-blind placebo-controlled multicenter studies it reduced itch significantly in comparison with placebo.

Nalfurafine hydrochloride has a good safety profile and is well tolerated. Its major adverse effect is insomnia. This drug is currently only available in Japan for HD patients with CKD pruritus [42,43].

Gabapentin, a gamma-aminobutyric acid analogue anticonvulsant, was found effective for uremic pruritus in a double-blind controlled study [44]. The investigators showed that 24/25 patients responded to 300 mg administered after dialysis three times a week. Manenti *et al.* made similar observations with a lower dose of 100 mg on a similar dosing schedule [45]. Pregabalin is another amino acid derivative of gamma-aminobutyric acid that is similar to gabapentin. It has better bioavailability and requires a lower dose. However, there are as yet no controlled studies on its use for uremic pruritus. Therefore, gabapentin remains the most effective treatment for CKD itch.

### Phototherapy

The efficacy of broadband ultraviolet B (UVB) phototherapy in pruritus of renal failure was first suggested by Gilchrist *et al.* in a large open study [46]. Since generalized pruritus abated even though only half of the body was treated, a systemic effect was inferred. A subsequent meta-analysis of the results of randomized controlled trials (RCTs) came to the conclusion that broadband UVB is the treatment of choice for moderate or severe uremic pruritus [47].

Narrowband UVB is less erythemogenic, and was reported in a small pilot study to reduce CKD pruritus [48].

### Other treatments

Other treatments that have been successfully used in anecdotal reports for CKD pruritus include thalidomide and butorphanol, a kappa opioid and  $\mu$ -antagonist [49,50].

### Drawback of current therapies

Opioid  $\mu$ -receptor antagonists carry a risk of hepatotoxicity, and they inactivate opioid pain killers that are being given concurrently. Kappa opioids cause insomnia.

Gabapentin is excreted by the kidney, and high doses may induce adverse neurotoxic effects such as somnolence, dizziness, and coma. Thus, patients should be started on a low dose (100 mg) and monitored closely.

### Implications for clinical practice

The causes of pruritus in CRF are obscure, so it is unsurprising that there are no highly effective treatments. Despite best efforts, treatment is often at best only moderately successful.

The current mainstay of therapy for pruritus of CRF includes emollients, topical anesthetics, low-dose oral gabapentin or UV phototherapy three times a week. Kappa opioids may be helpful for CRF pruritus.

#### Key points: pruritus of chronic renal failure

- Pruritus of CRF is a chronic debilitating disease that mostly affects patients on HD.
- The cause of the itch is probably multifactorial, and generally poorly responsive to treatment.
- Topical regimens include emollients and topical anesthetics, such as pramoxine and capsaicin, but these agents are difficult to employ over very large area.
- Broadband UV radiation, low-dose gabapentin, pregabalin, and kappa opioid agonists are effective treatments.

## Pruritus of cholestasis and hepatic disease

### Definition

This itch – often intense and unbearable in cholestasis – is frequently widespread; but unlike generalized pruritus due to other causes, symmetrical involvement of the palms of the hands and soles of the feet is common and typical [51]. When due to cholestasis, it is often, but not invariably, accompanied by jaundice. Patients usually rub rather than scratch, and secondary excoriation, eczematization, and skin infection are therefore less common than in pruritus of CRF.

### Incidence

Itching occurs in 20–25% of patients with cholestasis [52] and is severe and invariable in cholestasis due to primary biliary cirrhosis (PBC) [53]. It seems that the prevalence of itch in PBC is much higher than in other liver diseases [54].

### Etiology

Recognized causes of pruritus include PBC, primary sclerosing cholangitis, obstructive choledocholithiasis, carcinoma of the bile duct or head of the pancreas, and viral hepatitis. Less common

causes include cirrhosis. Cholestasis and associated itch can also be drug-induced [55]. The cause of the itching, originally thought to be due to bile acids, is now also believed to be due to increase in activity of lysophospholipase autotaxin and its product lysophosphatidic acid [56].

Other pruritogens involved in cholestatic itch are opioid peptides synthesized in the liver and acting on  $\mu$ -opioid receptors located mainly in the central nervous system [57].

### Prognosis

Relief of biliary obstruction by surgery or a stent causes rapid abatement of pruritus. In patients with itch due to parenchymal liver disease (e.g., such as hepatitis C infection, PBD), itching is variable and persistent, with a capricious response to treatment.

### Diagnosis

The combination of jaundice and generalized pruritus, with the skin being otherwise essentially normal, is highly suggestive of a cholestatic cause for the itch. However, cholestatic itching can occur without jaundice, as in pregnancy cholestasis. In such cases, the presence of elevated plasma bilirubin and alkaline phosphatase and bile acids in plasma and urine strengthens the diagnosis.

### Treatment aims

When an obstructive cause can be identified and relieved, treatment of the itch is symptomatic and short term. In patients in whom the pruritus is secondary to intrahepatic cholestasis, hepatitis, or cirrhosis, the aim is to alleviate or, if possible, abolish the itching.

### Outcomes

Amelioration or abolition of itching.

### What are the guiding principles in choosing treatment for pruritus of cholestasis or liver disease?

#### General measures

These include a cool environment, tepid showers, and wearing light, loose-fitting clothes.

Frequent application of a lotion of calamine with 1% menthol is also well appreciated by most patients.

#### Efficacy

Any extrahepatic obstruction of the biliary tract should be relieved, and will be followed by rapid remission of the pruritus. Intrahepatic cholestasis is more challenging to treat. In many patients, the frequency and intensity of cholestatic pruritus does not correlate with the severity of bile obstruction. Moreover, in many cholestatic patients, administration of bile acid resins does not improve itch. Oral antihistamines are generally ineffective. In selected cases in which pruritus is intractable and severe, liver transplantation should be considered.

Oral cholestyramine (4g administered before and after breakfast) is hallowed by tradition but not by controlled clinical trials [58]. Since it works by binding intestinal bile acids and other anions, thereby decreasing enterohepatic circulation, it is ineffective in the presence of total biliary obstruction.

Oral ursodeoxycholic acid 8–10g/day, a naturally occurring hydrophilic bile salt, was found to be effective in pruritus of PBC in only two of 11 trials reported in a meta-analysis of RCTs [59]. However, a recent meta-analysis of nine published trials for



intrahepatic cholestasis of pregnancy (ICP) showed that it is more effective than cholestyramine [60]. Also, in a head-to-head comparison it was shown to be more effective than cholestyramine [61].

Rifampicin, which induces cytochrome P-450 enzymes in the liver, thereby reducing putative liver-derived pruritogens, was found to be effective in the treatment of cholestatic pruritus at a dosage of 350–600 mg/day [62,63]. Recent meta-analysis of randomized trials revealed that rifampin is a safe and effective short-term treatment for cholestatic pruritus [64,65].

The oral opioid antagonists nalmefene (5–20 mg twice daily) and naltrexone (50 mg/day) were shown to be effective in reducing pruritus in two controlled studies, which both used a visual analogue scale and a scratching activity monitoring system to quantify itch [66,67]. A reduction in itch by 50–90% was seen in these studies. Naloxone, a parenterally administered opioid antagonist – infused at 0.2 µg/(kg min) – was also found to be effective in a double-blind, randomized, placebo-controlled trial [68].

Kappa opioid agonists that have less side effects, such as nalfurafine, have been proposed to be effective antipruritics for cholestatic pruritus [69]. Butorphanol inhaler, a kappa agonist and mu antagonist available in Europe and the USA, was reported to alleviate intractable itch of hepatitis C [50].

Selective serotonin antidepressants have been reported to be of some effect for cholestatic pruritus. In a double-randomized study, sertraline in doses of 75–100 mg has shown to be effective for cholestatic pruritus [70]. Paroxetine in dose of 20 mg has been reported to be effective for cholestatic itch [71].

Gabapentin, which is an effective therapy for different types of chronic itch, has not shown any efficacy for cholestatic pruritus in a double-blind placebo-controlled study [72].

Other treatment modalities advocated to include odansetron (8 mg daily orally in one RCT) [73].

Extracorporeal elimination of pruritogens has been used with different techniques, including plasma separation and the Molecular Adsorbent Recirculating System (MARS®; albumin liver dialysis), and reported in more than 20 patients to be effective for cholestatic itch [74,75].

Phototherapy with UVB has recently been reported to have reduced cholestatic itch by more than 60% in more than 70% of cholestatic pruritus patients with different types. The mean number of irradiations required to obtain this effect was  $26 \pm 17$  (average duration of phototherapy: 8 weeks) [76]. Other treatment modalities include an open study of bright-light therapy directed into the eyes up to 60 min twice daily [77].

### Drawbacks

Cholestyramine, although probably mildly effective, is unsatisfactory owing to poor patient compliance (due to the taste and constipation). Rifampicin and the opioid µ-receptor antagonists, although of proven effectiveness, are associated with a high frequency of liver toxicity. The latter also cause opioid withdrawal symptoms, which can be largely prevented by starting with a low dose and increasing gradually [78].

### Comments

Ursodeoxycholic acid seems to be the first-line therapy for cholestatic pruritus but has limited efficacy.

Rifampicin and opioid antagonists are effective in the treatment of cholestatic itch, but the incidence of adverse effects is high with rifampicin and opioid antagonists, and they should be used cautiously [79].

### Implications for clinical practice

Patients receiving active treatment for cholestatic pruritus with rifampicin or opioid antagonists should be regularly and frequently monitored for adverse effects, especially in the liver.

### Key points: pruritus of cholestasis and hepatic disease

- Where there is an identifiable obstruction, its removal will result in rapid relief of pruritus.
- Rifampicin and opioid antagonists are of proven value as second-line measures, but they should be used cautiously, owing to the frequency of adverse side effects.

## Pruritus in hematological diseases

### Definition

Itching is a frequently presenting symptom of Hodgkin's and non-Hodgkin lymphomas, cutaneous T-cell lymphomas (see also Chapter 34 on cutaneous T-cell lymphoma), polycythemia vera (PV), and occasionally also occurs in other hematological disorders, including myelodysplasia and lymphoblastic leukemia. Pruritus associated with hematological diseases is characteristically triggered by contact with water. Pruritus, often localized, also occurs in association with iron deficiency.

### Incidence

In Hodgkin's lymphoma, the incidence of itch occurs in 30% of patients [80]. More recent data obtained in a retrospective study at M.D. Anderson showed the incidence of itch in Hodgkin's lymphoma patients was 19% [81]. In PV, itching ranges between 31 and 48% of the patients [82,83]. Figures from an epidemiological study in Finland involving a survey of over 40 000 adults showed that 13.6% of iron-deficient men complained of frequent pruritus, contrasting with 5.3% in men who were not iron deficient ( $P < 0.001$ ) [84]. The corresponding figures for adult women were 7.4% and 5.1% ( $P < 0.01$ ).

### Etiology

The underlying pathophysiology of lymphoma and hematological-associated pruritus is poorly understood. Pruritus in PV is significantly associated with a low mean corpuscular volume and raised leukocyte count [82]. Other proposed pathogenetic factors include elevated plasma histamine levels and elevated tissue fibrinolytic activity [85]. The pathogenesis of itching in iron deficiency is unknown.

### Prognosis

Treatment of PV often improves the pruritus, but in 20% of patients the itch is persistent [86]. Symptomatic treatment also greatly improves the quality of life for affected patients. The benefits conferred by iron supplements in patients with pruritus associated with iron deficiency are unclear, since no controlled trials have been done.

## Diagnosis

Any patient complaining of pruritus triggered by contact with water at any temperature, and without a rash, should be suspected of having PV or myelodysplastic syndrome and hematological malignancies. The diagnosis of lymphoma is confirmed by lymph node biopsy or organ biopsy. The diagnosis is confirmed by demonstrating raised hemoglobin, hematocrit, red cell mass, platelet count, and leukocytosis. Iron deficiency is established by demonstrating a lowered serum iron and high total iron-binding capacity.

## Treatment aims

Itch in lymphoma and itch in PV are distressing symptoms, and the aim should be to achieve its abolition or at least reduction to tolerable levels. Iron deficiency should be corrected in order to ameliorate itching.

## Outcomes

Reduction or abolition of itching.

## What treatments are available for pruritus of polycythemia vera?

### General measures

Pruritus in PV, sometimes water-induced ("bath-time itch"), is distressing and disabling. Because there is often no visible accompanying eruption, the sufferer receives scant sympathy. Explaining this to family members and caregivers forms an important part of the management of these patients.

### Efficacy

Although blood histamine levels are often elevated,  $H_1$  antihistamines are rarely effective.

Selective serotonin reuptake inhibitors (SSRIs), paroxetine 20 mg/day and fluoxetine 10 mg/day, were shown to effectively reduce itch in eight out of 10 patients in an open-label trial [87].

Aspirin has anecdotally been found effective in some patients with PV [88]. Narrowband UVB administered three times weekly (10 patients) and photochemotherapy with 8-methoxypsoralen-ultraviolet A (PUVA) two or three times weekly, with 15 treatments (in 11 patients) have been claimed to be effective in open studies of PV [89,90].

Interferon alfa ( $IFN-\alpha$ ) is an effective drug for PV, and has been noted to be effective in the control of PV-associated pruritus [88,91].

A Janus kinase inhibitor 2 ( $JAK1/2$ ) has been recently tested in a phase II study involving advanced PV and essential thrombocytosis patients. All patients with pruritus reported a rapid and sustained reduction of this symptom [92].

A phase I study using a selective  $JAK2$  inhibitor (TG101348) reported a significant reduction in constitutional symptoms, including pruritus [93].

An inhibitor of the mammalian target of rapamycin that was administered to a cohort of nine patients with aquagenic pruritus with primary myelofibrosis and post-PV myelofibrosis resulted in complete resolution of itch in all patients [223]. The exact mechanism by which these agents produce a reduction in the pruritus is currently unknown.

The efficacy of oral iron supplements in patients with pruritus and iron deficiency has not been established in clinical trials.

### Drawbacks

PUVA and narrowband UVB are usually well tolerated, but relapse occurs within weeks of the end of treatment.

## Comments

Although the published evidence is weak, it is likely that phototherapy or photochemotherapy is effective in ameliorating pruritus in some patients with PV. The new  $JAK$  inhibitors seem promising for treatment of PV itch. The value of iron supplements in the treatment of pruritus associated with iron deficiency is questionable.

## Implications for clinical practice

Phototherapy and photochemotherapy offer safe and often effective, although temporary, relief of pruritus in PV.

### Key points: pruritus in polycythemia vera and patients with iron deficiency

- Pruritus in PV, often triggered by contact with water, can be effectively relieved in some patients using either narrowband UVB or PUVA.
- Low-dose SSRIs are effective therapy for PV and myelofibrosis pruritus.
- The  $JAK$  inhibitors seem to have antipruritic effects, but further controlled trials are needed to explain their role in pruritus treatment.

## Pruritus of endocrine diseases

### Definition

#### Thyroid disorders

Generalized pruritus is seen commonly in patients with hyperthyroidism, particularly in cases of thyrotoxicosis of Graves' disease [94]. Hypothyroidism is less frequently associated with itch, and is associated with skin xerosis [95].

#### Diabetes

Generalized itching does not appear to occur at increased frequency in diabetic patients [94]. However, pruritus due to other disorders in diabetic patients, including dermatophyte infections, xerosis, diabetic neuropathy, or *Candida* infections (such as may be seen in the anogenital region), may occur [94]. In particular, diabetic neuropathy may account for localized itch without rash. A recent large study from Japan reported truncal itching in 11% of patients with type 2 diabetes. Patients with abnormal sensation were at risk for this type of itch [96].

Pruritus in diabetics is commonly noted in the anogenital area in association with candida intertrigo. It may be more widespread if diabetes is complicated by CRF in perforating collagenosis, such as in Kyrle's disease. In contrast, pruritus in hyperthyroidism is usually widespread, and may be a severe presenting symptom.

### Incidence/prevalence

Most textbooks cite diabetes as an important cause of chronic generalized pruritus. This belief dates from 1927, when a study of the skin in 500 patients with diabetes reported an incidence of pruritus of 6.5%, with about half of the cases being generalized; however, there was no control group [97]. A more recent study of 300 diabetic and 100 matched nondiabetic patients reported that pruritus vulvae was more common in the diabetic group (18.4% vs 5.6% in controls), but the frequency of generalized pruritus did not differ between the two groups [98].

Although itching is a widely recognized symptom of overactive and underactive thyroid disease, figures for the incidence and prevalence are scarce. A recent study in 120 hyperthyroid patients reported pruritus, often generalized, in 60% [94].

In hypothyroidism, the incidence of pruritus is unknown, but it seems rare.

### Etiology

Pruritus in diabetes is commonly localized, it is frequently noted in the anogenital area due to candidiasis, and is directly related to poor diabetes control [98]. Occasionally, it can be due to diabetic neuropathy, xerosis, or CRF. The cause of itching in thyrotoxicosis is unknown.

### Prognosis

The prognosis of pruritus in diabetes depends on the effectiveness of control of underlying hyperglycemia. Correction of thyroid dysfunction leads to remission of the itch in thyrotoxicosis.

### Treatment aims

The achievable aim should be complete abolition of localized pruritus in diabetics, and of generalized pruritus in thyrotoxicosis. The itching in hypothyroidism can be reduced, but complete relief is often difficult to attain.

### Outcomes

Freedom from itching in diabetics and patients with thyrotoxicosis.

### How can localized itch of diabetics be effectively treated? How should the patient with generalized itching due to hypothyroidism or hyperthyroidism be managed?

#### General measures

Anogenital pruritus in diabetics is helped by careful drying after bathing, use of loose-fitting underwear, and, most importantly, adequate control of diabetes (also see section on “Anogenital pruritus”). Mitigation of generalized pruritus of thyrotoxicosis can be achieved by measures to cool the warm, moist itchy skin. These include wearing light clothing, tepid showering, a cool ambient temperature, and calamine lotion.

#### Efficacy

There are no clinical trials of treatment of diabetic pruritus. For the anogenital itch, since the majority are due to candidiasis, anti-*Candida* treatment using topical imidazole antifungals is usually effective if combined with adequate management of the diabetes. Oral anti-*Candida* agents may also be required. Pruritus in hyperthyroidism should be treated by correction of thyroid function.

#### Drawbacks

Since diabetics are strongly predisposed to mucocutaneous candidiasis, the relapse rate of anogenital candidosis and its associated pruritus is high even if the diabetes is controlled.

#### Comments

Oral antihistamines are ineffective in relieving of pruritus due to endocrine disease. Topical antihistamines and local anesthetics should be avoided in anogenital pruritus in diabetics, owing to risk

of sensitization. Topical corticosteroids should be used cautiously and for a limited time.

### Implications for clinical practice

Sustained remission of anogenital pruritus of diabetes mellitus can be difficult to achieve, especially in women with vulvo-vaginal candidosis. Reservoirs of reinfection, such as *Candida* paronychia, also need to be vigorously treated (also see section on “Anogenital pruritus”).

#### Key points: pruritus in thyroid disease and diabetes mellitus

- In diabetes, pruritus is usually localized and could be associated with diabetic neuropathy.
- Anogenital itch is common in diabetics and is frequently due to candidiasis.
- In hyperthyroidism, pruritus is generalized and multifactorial.
- Treatment of diabetic anogenital pruritus includes adequate control of diabetes, combined with local or occasionally systemic anti-*Candida* therapy.
- Apart from general measures, the treatment of pruritus of thyrotoxicosis consists of correcting the thyroid dysfunction.

## Anogenital pruritus

### Definition

This is defined as chronic localized intense pruritus affecting the perianal area (pruritus ani), scrotum (scrotal pruritus), and the vulva (pruritus vulvae). Although frequently idiopathic, anogenital pruritus may be a manifestation of dermatosis or systemic or neuropathic disease. If persistent, it leads to secondary skin lesions (e.g., lichenification locally), and it also causes severe distress and sleep disturbance.

### Incidence/prevalence

Pruritus ani occurs in 1–5% of the adult population, and males are more commonly affected than females [99]. Precise figures for the incidence and prevalence of pruritus vulvae are unavailable. It can occur at any age, but in its chronic presentation it is common post-menopausally [100].

In 20 patients suffering from anogenital pruritus without any skin diseases or anorectal pathology, lumbo-sacral radiculopathy and degenerative changes in the lower spine were confirmed in 80% of cases [101].

Itching was the single most frequent presenting symptom occurring in 70% of patients consulting a clinic for vulvar disease [102].

Out of 93 women with psoriasis, 44.1% experience vulvar discomfort, including 19.4% with itch, 10.8% with burning, and 14% with both itching and burning sensations. Psoriatic lesions were present on the vulva in 23.7% of subjects. There were no significant correlations between burning/itching intensity and global psoriasis severity [103]. Vulvar itching was significantly more common in diabetic women (18.4%) than in controls. Itching in the genital and perianal area is significantly more common in diabetic women and is significantly associated with poor diabetes control [98].

## Etiology

Common dermatoses that involve the anogenital area and cause pruritus include psoriasis, atopic dermatitis, lichen sclerosus, lichen planus, scabies, pediculosis, allergic contact dermatitis (especially with perfumed soaps; 18 of 40 patients with pruritus ani had positive patch tests) [104], and seborrheic dermatitis (also see Chapter 25). Dermatitis medicamentosa due to contact allergic sensitization to long-continued topical application of antipruritics, especially local anesthetics and antihistamines, is common [105]. Local problems causing pruritus include threadworms, warts, hemorrhoids, lichen simplex chronicus, carcinoma, and urinary or fecal incontinence. In women, vaginitis – especially vaginal candidiasis – is an important local cause, and estrogen deficiency is an important systemic cause. In one study of 1104 patients with pruritus vulvae, 946 (85%) had candidal or trichomonal vaginitis [106]. Diabetes mellitus is a common systemic cause in both sexes. Vulvar dermatitis (frequently leading to pruritus vulvae) is frequently associated with atopic diathesis [107].

A prospective study in 42 women with pruritus vulvae and 42 asymptomatic controls did not provide evidence to support the routine determination of iron status in patients presenting with pruritus vulvae [108]. Psychogenic factors (“stress”) are often cited in cases in which none of the above causes are found, but stress is probably a frequent cause or a co-factor.

## Prognosis

Anogenital pruritus is characteristically chronic and poorly responsive to treatment, even when a cause has been identified and treated. The itch–scratch cycle is especially hard to break at this site.

## Diagnostic tests

Examination of the skin and mucous membranes, including the genito-anal region, is necessary. Skin biopsy for diagnosis of a dermatosis may be required. Depending on the clinical findings, appropriate tests to identify bacteria, fungi, or candida should be performed. Anal or anogenital pruritus requires stool investigations (e.g., parasites, giardia lamblia, worm eggs), as well as proctoscopy, rectoscopy, and perhaps colonoscopy, depending on the findings. Gynecological examination is required in genital pruritus. In case of suspected contact dermatitis, a careful history of topicals used is essential, and patch testing may be necessary. In 50 women with vulvar pruritus, 52% had at least one positive patch-test reaction to allergens such as cosmetics, preservatives, and topical medications [109]. If a neurological etiology is suspected (especially in chronic back pain patients), magnet resonance tomography of the spine (especially lumbo-sacral spine) is necessary to rule out stenosis of the intervertebral foramen or protrusion of the discs. In severe cases of chronic anal, genital, or anogenital itch without any underlying etiology or no improvement by therapy or counseling, a psychiatrist may be necessary.

## Treatment aims

Treatment should be targeted at breaking the itch–scratch cycle. Breaking the cycle allows restoration of effective stratum corneum barrier function.

## Outcomes

Effective treatment should lead to gradual lessening of the compulsive desire to rub or scratch, with accompanying resolution of lichenification, pigmentation, and excoriation. Sleep disturbance should diminish. Restoration of an effective barrier function

enables the anogenital skin to resist normal “wear and tear” as well as minor irritancy.

## What are the roles of local and systemic treatments in the management of anogenital pruritus?

### General measures

Overenthusiastic cleansing and use of irritant toiletries, perfumed soaps, foam baths, or sensitizing topical medicaments should be discontinued. The anogenital area should be washed regularly with plain water and air dried or gently dabbed with cotton wool. For pruritus vulvae, wiping should always be from front to back. In severe cases of anogenital pruritus, sitz baths (warm plain water hip baths) bring about rapid relief. Ointments are preferable to creams, owing to the presence of potentially irritant preservatives in the latter. Silicone barrier and zinc oxide ointments help retain moisture in affected skin, thereby enhancing healing.

### Efficacy

When anogenital pruritus is a manifestation of a primary skin disease or local lesion such as hemorrhoids, threadworms, or vaginitis, apart from general measures, the management is that of the causative dermatosis or local pathology. Adequate control of underlying diabetes mellitus is essential, together with treatment of the invariable underlying candidosis. In postmenopausal pruritus vulvae, systemic hormone replacement therapy should be considered.

Vaginal candidosis is also an important cause of pruritus vulvae in nondiabetic women. In one study, 17 of 38 women (45%) with pruritus vulvae were found to have *Candida albicans* infection [110]. Although underlying local or systemic disease can be identified in many patients, the cause in some patients with pruritus vulvae is elusive (idiopathic vulval pruritus). Most of these patients receive topical steroid treatment. There are no controlled trials, but one open study of 65 patients showed that 56 of these reported complete relief in 2 days following topical fluocinolone acetonide [111]. Intralesional injection of triamcinolone has been proposed for recalcitrant pruritus vulvae. Of 45 patients, 35 experienced relief for at least 1 month (mean 5.8 months) following a single injection [112]. For exceptionally resistant and handicapped patients, multiple local intradermal injections of ethanol have been reported to be effective by several authors. In one double-blind study [113], 14 of 17 patients reported complete relief by undermining the skin of the vulva, the vaginal mucosa, and perianal skin [114,115]. Of 16 women, 15 experienced immediate relief of itching and no relapse occurred after follow-up periods ranging from 3 months to 3 years.

Topical corticosteroids are the standard treatment for perianal pruritus if it persists despite the removal or treatment of the underlying causes, or when no cause can be found. Controlled trials are lacking, but in a recent study in idiopathic perianal pruritus one group of 28 patients applied topical methylprednisolone cream twice daily for 2 weeks, with a second group of 32 patients using a liquid cleanser only [116]. The results were similar in the two groups, with over 90% of patients responding ( $P > 0.05$ ). Intralesional triamcinolone has also been used for recalcitrant pruritus ani. Nineteen patients with idiopathic pruritus ani were treated with triamcinolone hexacetonide intralesionally for 4 weeks (dosage 5–20 mg weekly) [117]. Very good improvement occurred in 14 patients and fair improvement in two. No skin atrophy was noted. Fifteen patients with anogenital pruritus were treated with paravertebral injections at the level of L5–S1 (2.5 mL triamcinolone



acetone 10 mg/mL, 2.5 mL lidocaine 1% divided into five or six separate injections). The degree of pruritus was significantly reduced 2–4 weeks after the injections [101].

Topical capsaicin is a recognized treatment for various types of localized pruritus. A recent double-blind placebo-controlled crossover study compared capsaicin 0.006% cream with 1% menthol cream in idiopathic intractable pruritus ani [118]. Use of the capsaicin cream three times daily for a month led to partial relief of pruritus in 31 of 44 patients, and the menthol cream was invariably ineffective. Intralesional 5% phenol has also been used with success in patients with idiopathic pruritus ani resistant to conventional modalities. In an open study of 67 patients, 62 (92.5%) experienced complete relief [119]. Five of them subsequently relapsed, but sustained remission followed after a repeat injection.

According to a systematic review, limited evidence supports the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital lichen sclerosis [120]. Clobetasol propionate 0.05% cream and pimecrolimus 0.1% cream were both effective in relieving pruritus and burning pain. There were no significant differences between the two substances [121].

### Drawbacks

Potent topical corticosteroids are widely prescribed for most types of anogenital pruritus, often for long periods of time. Although usually effective, they may mask underlying primary pathology, including neoplasia, infection, and allergic contact sensitization. Local steroid atrophy may also occur. Similar caveats apply to intralesional triamcinolone injections. Although safe, patient compliance with topical capsaicin is poor owing to its burning action. Experience with intralesional injection of ethanol or phenol is too limited to warrant consideration except in the most intractable cases.

### Comments

Careful history-taking, clinical examination, and investigation of patients with pruritus vulvae or ani will frequently be rewarded by discovery of an underlying primary cause. Embarking on prolonged topical potent steroid application should be delayed until these avenues have been thoroughly explored.

### Implications for clinical practice

A patient presenting with pruritus ani or vulvae should also always undergo rectal and/or vaginal examination. Patients with a long history of poor response to topical medications should be considered to have dermatitis medicamentosa until proved otherwise by patch testing.

#### Key points: anogenital pruritus

- Anogenital pruritus is usually a symptom of underlying skin disease, local disease, systemic disease, or lumbo-sacral degenerative changes.
- Diabetes mellitus, candidosis, and rectal or vaginal malignancy should be sought and treated.
- Contact dermatitis is common, and patch testing should be carried out in treatment-resistant patients.
- General measures, especially avoidance of irritants and the use of skin-friendly anogenital hygiene, encourage restoration of the stratum corneum barrier.
- In idiopathic cases, topical corticosteroids may be helpful, but they may mask malignancy and other underlying disease.

## Drug-induced itch

### Definition

Drug-induced itch is defined as generalized itching without skin lesions, caused by a drug. Drug-induced itch can be acute (<6 weeks), most frequently caused by opioids and chloroquine [122]. It usually resolves after stopping the drug. Chronic itch (>6 weeks) usually does not spontaneously stop after withdrawal of the drug [122]. It is frequently caused by hydroxyethyl starch (HES).

### Incidence/prevalence

In the Boston Collaborative Drug Surveillance Program studies that were published in the *Journal of the American Medical Association*, drug-induced itch without a rash accounted for approximately 5% of adverse cutaneous reaction in prospectively followed hospitalized patients. Adverse cutaneous reactions occurred in 3% of the patients [123,124], except for itch induced by HES. The latter is described as occurring in 12.6–44% of patients treated with HES [125–127]. Opioid-induced itch is a common problem after epidural and intrathecal administration of opioids, usually localized on the face, neck, and upper thorax. No reliable data are available on the incidence and prevalence rates. The variation in the incidence has been reported to range from 50 to 90% [128,129].

There are no epidemiological data on how frequently drugs cause itch in a population of itch patients.

### Etiology

Many drugs must be used with caution in human immunodeficiency virus (HIV) patients, who may be susceptible to hypersensitivity reactions, drug interactions, and idiosyncratic reactions. Some of them may present with pruritus without skin lesions. It has recently been shown that spinal opioid-induced itch is evoked independently of opioid-induced analgesia by signaling through an opioid receptor splice isoform expressed in itch-mediating spinal neurons [130].

A great number of drugs ranging from antihypertensive drugs to antiepileptic drugs need to be considered as a possible cause of pruritus [122].

Severe generalized or localized itching can be induced via the following mechanisms:

- cholestasis – for example, oral contraceptives or other estrogens, captopril, chlorpromazine, valproic acid, erythromycin, sulfonamide, minocycline;
- hepatotoxicity – oral contraceptives or other estrogens, testosterone and other anabolic steroids, phenothiazine, phenytoin, acetaminophen, isoniazid, halothane, sulfonamide, minocycline, cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib);
- deposition – HES;
- xerosis cutis – retinoids, beta-blockers, tamoxifen, busulfan, clofibrate;
- phototoxicity – 8-methoxypsoralen, doxycycline;
- neurologic – tramadol, codeine, cocaine, morphine, fentanyl, topiramate;
- idiopathic – chloroquine, quinidine, clonidine, gold salts, lithium, angiotensin-converting enzyme inhibitors;
- new anticancer drugs (i.e., epidermal growth factor receptor inhibitors), as well as anti-melanoma drugs (i.e., ipilimumab).

## Prognosis

If the offending drug is discontinued, the itching resolves. There are no studies on the prognosis, except for HES-induced itch. The mean duration of HES-induced itching is 15 months, mainly depending on the amount of HES deposited. Tissue deposition of HES is dose dependent and time dependent [131]. Neural deposition of HES was confined to a total dose of HES exceeding 210 g. After administration of 414 g, 32% of the patients suffered from pruritus, in comparison with 1% after a dose of 150 g [125,132].

## Diagnostic tests

In HES-induced itch, a skin biopsy with immunoelectron microscopy may demonstrate HES deposits in the skin.

## Aims of treatment

The aim of treatment is to abolish or reduce itching.

## Relevant outcomes

- Abolition of drug-induced itch.
- Prevention of drug-induced itch.

## Are there any drugs more likely to induce pruritus? Are there any treatment options other than discontinuing the offending drug?

### Evidence summary: efficacy

There are no controlled trials investigating the mechanisms and treatment options for drug-induced itch, except for opioid-induced itch. The literature shows that cholestasis and hepatotoxicity appear to be the most frequently reported triggers of this type of pruritus.

In HES-induced itch, topical capsaicin therapy at concentrations ranging from 0.025 to 0.5% four to six times daily showed antipruritic potency in a case report [133] and case series [134]. Single patients were reported to respond to oral naltrexone 50 mg daily in HES-induced itch [135,136]. Two cases of intractable pruritus in drug-induced cholestasis were successfully treated by extracorporeal albumin dialysis using MARS [137].

According to a quantitative systematic review of randomized trials on the pharmacological control of opioid-induced pruritus, there is a lack of valid data on the efficacy of interventions for the treatment of established pruritus [138]. Naloxone 0.25 µg/(kg h) was found to be efficacious in relieving postoperative pruritus in children and adolescents in a double-blind, prospective, randomized controlled study [139]. Naloxone infusion rates >1 µg/(kg h) significantly reduced the incidence of opioid-induced itch in postoperative pediatric patients receiving morphine [140].

Celecoxib 200 mg failed to relieve pruritus in a prospective randomized placebo-controlled trial involving 60 women undergoing cesarean section [141].

Naloxone 2 µg/(kg h) intravenously (i.v.), naltrexone 6 mg orally, nalbuphine i.v. (the optimal dose remains to be determined), and droperidol 2.5 mg or 5 mg i.v. or epidurally are effective in preventing opioid-induced pruritus [138,139]. The optimal dose is one that provides adequate relief of pruritus without increasing pain scores. There was a lack of evidence for any antipruritic efficacy with prophylactic propofol, epidural and intrathecal epinephrine, epidural clonidine, epidural prednisone, intravenous ondansetron, and intramuscular hydroxyzine [138]. A case report suggests rifampicin 300 mg i.v. twice daily in pruritus after morphine treatment in a cancer patient [142].

## Key points: drug-induced itch

- Drug-induced pruritus has multiple mechanisms. The treatment of drug-induced pruritus centers on discontinuation of the triggering drug.
- To prevent opioid-induced itch, naloxone, naltrexone, nalbuphine, and droperidol are efficacious.
- According to case reports, topical capsaicin therapy and oral naltrexone may be used to treat HES-induced pruritus.

## Human immunodeficiency virus and itch

### Definition

HIV-related itch is defined as generalized or localized itching in patients with HIV infection or acquired immune deficiency syndrome (AIDS).

### Incidence/prevalence

Itching is a very common symptom in this population, but epidemiological data about the incidence and prevalence of itch in HIV and AIDS populations are scarce. A recent study in 897 American HIV-infected patients revealed a pruritus prevalence rate of 6% [143]. HIV viral loads higher than 55 000 copies/mL had a higher prevalence of pruritus [143]. A recent study from Spain revealed that 31% of HIV patients attending a skin health program reported pruritus [144]. When the prevalence of pruritus in 310 patients with chronic HIV and hepatitis B and C virus infection was prospectively determined, the prevalence rate was 28% in patients with hepatitis C and HIV and 25% in those with hepatitis B and HIV [145]. When 84 Ugandan pruritus patients were investigated, 19% were found to be HIV positive [4].

### Etiology

HIV/AIDS patients are prone to develop a number of pruritic dermatoses [38,146–148]. The most common causes of HIV itch are skin xerosis, papular pruritic eruptions and prurigo of HIV, seborrheic dermatitis and cutaneous infections as tinea, folliculitis, and insect bite reactions. Other causes include photosensitive and drug reactions [149].

Systemic causes of pruritus in HIV are relatively uncommon, but may occur in HIV nephropathy, hepatic failure due to hepatitis B or C, and systemic lymphoma [38,146,147].

Pruritic papules of HIV have been found to be highly associated with arthropod bites in one cross-sectional study [150].

Severe pruritus may lead to secondary scratch lesions; for example, such as lichenification and prurigo nodularis. Lichenification is often triggered by other pruritic dermatoses. Prurigo nodularis can be caused by HIV-related dermatoses or HIV-related systemic diseases, but may also occur without any known cause. Generalized asteatosis clinically presents as xerosis or dry skin, accompanied by pruritus. It increases with disease progression, and CD4 counts decline [146].

As many as half of AIDS patients may never have specific causative or categoric diagnoses identified. Some authors term this “idiopathic pruritus” [146]. In these cases, it is most likely that itching is directly related to the HIV infection – for example, HIV viral load, immune dysregulation, reduced Th1, increased Th2, increasing levels of immunoglobulin A and immunoglobulin E (IgE), and increased eosinophils [144,151].

## Prognosis

The prognosis depends on the prognosis of the HIV infection and on the stage of the AIDS disease, as well as on optimum antiviral therapy.

## Diagnostic tests

The tests performed depend on the relevant differential diagnoses concerning the etiology. They may include HIV viral load, CD4 count, IgE, eosinophils, bile acids, transaminases, alkaline phosphatase, creatinine, blood urea nitrogen, and radiographic and sonographic examinations.

## Aims of treatment

Abolition of itching, reducing ichthyosis, reducing discomfort, improving the quality of life.

## Relevant outcomes

Abolition of itch, improvement of the quality of life.

## Are there any treatment options for human immunodeficiency virus-induced itch? Is one therapy superior to the others in improving quality of life in human immunodeficiency virus-induced itch?

### Evidence summary: efficacy

In a controlled but nonrandomized study, treatment of pruritus in HIV-1 disease did not reveal any difference between indomethacin 25 mg t.i.d., pentoxifylline 400 mg t.i.d., hydroxyzine hydrochloride 25 mg t.i.d., and 0.025% triamcinolone lotion (120 mL/week) [152].

In a noncontrolled, nonrandomized study, UVB phototherapy produced significant relief of pruritus and improved the quality of life in HIV-positive patients suffering from primary pruritus ( $n = 7$ ) and pruritic eosinophilic folliculitis [153]. The safety of phototherapy in HIV-positive patients has been debated, but it is considered to be safe [154,155].

Thalidomide has been used to relieve HIV-related pruritus in the setting of prurigo nodularis. A randomized study in 10 HIV patients suffering from prurigo nodularis showed a greater than 50% response in reduction of itch over 3.4 months when thalidomide was taken for longer than 1 month (eight of the 10 patients). The dosage ranged from 33 to 200 mg daily. Three patients developed thalidomide peripheral neuropathy [148].

A case report describes the use of hypnosis in the treatment of generalized itching in three HIV-positive men [156].

### Key points: human immunodeficiency virus and itch

- Pruritus is an important cause of discomfort and morbidity in HIV and AIDS patients.
- Treatment of pruritus in HIV and AIDS depends on the underlying etiology. Patients need careful evaluation in order to determine the underlying cause. In these cases, causative treatment is possible (e.g., treatment of an underlying systemic cause, treatment of underlying specific dermatoses, discontinuation of a drug).
- In pruritus that is not related to a specific dermatological or systemic disease, optimal antiviral treatment is best.
- Very limited data suggesting that symptomatic relief can be achieved with UVB phototherapy and that thalidomide may be helpful for pruritus associated with HIV-related prurigo nodularis need confirmation.

## Psychogenic itch

### Definition

Psychogenic itch refers to pruritus associated with psychiatric diseases and psychological factors (e.g., the delusional state of parasitophobia or neurotic excoriations). It may be generalized or localized.

### Incidence/prevalence

There are no data on the incidence and prevalence of psychogenic itch. It is estimated that psychogenic excoriation occurs in 2% of dermatology clinic patients [157]. One study showed >70% of itch patients had a psychiatric comorbidity or psychosomatic cofactors [158]. Another study demonstrated 22% of itch patients to have a psychiatric disease [159]. The occurrence of itching of the face was significantly more common in psychogenic itch [159]. Itching occurred in 32–42% of hospitalized psychiatric patients. When itching dermatoses and systemic causes were excluded [160,161], itching was experienced by 17.5% of psychiatric inpatient during a depressive episode [162]. It disappeared in all depressive patients with co-occurring itch during treatment with antidepressants [162].

### Etiology

Depression, anxiety, and schizophrenia have been described as causes of psychogenic itch. Neurotic excoriations and the delusional state of parasitophobia can be accompanied by psychogenic itch. Neurotic excoriations are characterized by excessive scratching and picking of normal skin, but this is not necessarily associated with pruritus. One study revealed that 58% of patients with psychogenic excoriations had a current major depressive syndrome and that 45% of patients with psychogenic excoriations had obsessive-compulsive disorder [163].

### Prognosis

There are no data on the prognosis of psychogenic itch. It is most likely that the prognosis depends on the underlying psychiatric disease and its treatment.

### Diagnostic tests

Psychiatric consultation and counseling for diagnosis or verification of the underlying psychiatric disease are necessary. Diagnostic criteria from the French Psychodermatology Group were proposed and validated [164,165]. Three compulsory criteria (localized or generalized itch without primary skin lesions, duration >6 weeks, no somatic cause) and optional criteria (three out of seven required) should be present; for example, a chronological relationship with one or several life events, variations in intensity associated with stress, predominance during rest or inaction, improvement by psychotropic drugs [164].

### Aims of treatment

Abolition of itching, reducing discomfort, improving the quality of life.

### Relevant outcomes

Abolition of itch and improving the quality of life.

## Which treatment options are efficacious for psychogenic itch?

### Evidence summary: efficacy

There are no controlled trials investigating the treatment of psychogenic itch. SSRIs, such as paroxetine 20 or 30 mg daily or fluoxetine 20 mg daily, showed efficacy in case reports [166,167]. In elderly patients, cardiac side effects may occur, so these drugs should therefore be applied with caution.

Mirtazapine, a nonadrenergic and specific serotonergic antidepressant, was associated with significant relief in a case of chronic neurotic excoriations at a dosage of 15 mg/day [168]. Dry mouth, sedation, and weight gain are the most commonly reported side effects, but its advantages are once-daily dosing and its lack of addictive potential.

There are no controlled trials of behavioral or psychotherapeutic treatments for neurotic excoriations. In case reports, behavioral techniques such as “habit reversal” have been found to be effective [157].

Narrowband UVB showed improvement in 70% of patients with resistant psychogenic excoriations in a case series [169].

### Key points: psychogenic itch

- Treatment of psychogenic pruritus depends on the underlying etiology.
- Paroxetine and mirtazapine were found to be useful in case reports of psychogenic pruritus and neurotic excoriations.

## Itch and senescence

### Definition

Generalized or localized itching in patients over the age of 65 may be called senescent pruritus or elderly itching.

### Incidence/prevalence

A Turkish study investigating 4099 elderly patients found that pruritus ranked first in the distribution of skin diseases, with 11.5% complaining about pruritus. Women were more frequently affected (12.0%) than men (11.2%) [170]. With regard to the age group, patients aged over 85 had the highest prevalence rate (19.5%). With regard to seasonal variations, senescent pruritus was among the five most frequent diagnoses in all seasons and was most frequent in winter (12.8%) and fall (12.7%) [170]. Pruritic diseases were the most common in a study from Thailand (41%) that identified xerosis (which for the authors was identical with senescent pruritus) as being the most frequent condition (38.9%) in a total of 149 elderly patients [171].

One population-based study found a significant association between age and lifetime prevalence of chronic itch [172].

### Etiology

Aging skin is characterized by a decline in the regular functions of the skin (e.g., cell replacement capacity, barrier function, immune

responsiveness, sebum production, sweat production, sensory perception, and wound healing). Current theories of senescent pruritus range from xerosis cutis to degenerative changes in the peripheral nerve endings. One study detected increased histamine release and skin hypersensitivity to histamine in pruritus of the elderly [173].

### Prognosis

No data are available on the prognosis.

### Diagnostic tests

The elderly are more likely to take multiple medications that may cause itching (see also the earlier section on “Drug-induced itch”). As the elderly are also more likely to have systemic diseases that can potentially cause itching, a precise dermatological and general examination should exclude an underlying systemic disorder. Laboratory studies may include erythrocyte sedimentation rate, a complete blood cell count with differential leukocyte count, blood urea nitrogen, creatinine, liver transaminases, alkaline phosphatase, bilirubin, thyroid function test, serum iron, ferritin, and radiographic and sonographic examinations (also see reference [21]). The diagnosis of senescent pruritus is made on the basis of chronic pruritus after other causes of itching have been excluded.

### Aims of treatment

Abolition of itching, reducing discomfort, improving the quality of life.

### Relevant outcomes

Abolition of itch.

## What are the major causes of senescent pruritus? Are there any effective therapies for itch in the elderly?

### Evidence summary

Therapy depends on an underlying systemic disease, if present.

A double-blind placebo-controlled trial including 19 patients with senile pruritus who were treated with oxatamide 30 mg b.i.d. for 2 months showed complete suppression or marked improvement of pruritus in 79% of the patients [174].

A controlled nonrandomized study in 60 patients suffering from senescent pruritus and 20 control individuals (20 patients unaffected by pruritus in the elderly, aged 63–83, median age 77) was carried out and showed complete or marked improvement in 41% of patients treated with loratadine 10 mg and in 38% of patients treated with terfenadine 120 mg orally. There were no significant differences between the groups [173]. Exact results for the control group were not given in the study.

Ten patients with essential senescent pruritus were treated with ciclosporin A 5 mg/kg body weight per day for 8 weeks in an open uncontrolled study. Ciclosporin A treatment significantly reduced the itch intensity in all patients. In eight patients, pruritus ceased in the fourth week of treatment. No relapses occurred until 3 months after discontinuation, except for one patient suffering from mild localized pruritus [175].

From the clinical point of view, it is well known that the elderly frequently suffer from itching caused by xerosis cutis, asteatotic dermatitis, or stasis dermatitis. Topical emollients (also with urea or anesthetic agents) are usually very helpful, but there is a paucity of published quantitative evidence of their role.



**Key points: itch and senescence**

- Pruritus in the elderly is quite frequent, with a gradually increasing prevalence in increasing age.
- Therapy includes treatment of an underlying systemic disease, if present, and use of emollients, especially in xerosis cutis.
- Everyday experience suggests that xerosis cutis plays an important role.

**Neuropathic itch****Definition**

Neuropathic itch is defined as pruritus that is caused by a disease at any point along the peripheral or central pathway of the nervous system.

**Incidence/prevalence**

Itching is reported by up to 58% of patients suffering from herpes zoster and up to 30% of patients suffering of postherpetic neuralgia, mainly affecting the head, face, and neck [176,177]. There are no epidemiological data on, for example, notalgia paresthetica, brachioradial pruritus, or pruritus in multiple sclerosis.

**Etiology**

Notalgia paresthetica, brachioradial pruritus, postherpetic neuralgia/itch, pruritus in multiple sclerosis, trigeminal trophic syndrome (TTS), and itch post cerebral vascular accident (CVA) and in Jakob–Creutzfeldt demyelinating syndrome [178] are clinical forms of neuropathic itch.

Notalgia paresthetica is characterized as localized pruritus medial to the scapular area, frequently accompanied by a hyperpigmented patch. It is described as being caused by degenerative changes in the vertebrae corresponding to the dermatome of itching [179]. When 43 patients with notalgia paresthetica were evaluated, 61% had spinal changes judged to be relevant [180]. The striking correlation between the localization of notalgia paresthetica and spinal pathology suggests that spinal nerve entrapment may contribute to notalgia paresthetica [179,180]. A retrospective study with 65 patients suffering from notalgia paresthetica revealed 32.3% with stenosis and 47.7% with degenerations of the spinal column [181]. However, the significant reduction in intra-epidermal nerve fiber density suggests that damage to the peripheral nerves is a more important etiological factor than spinal changes in notalgia paresthetica [181].

Brachioradial pruritus is characterized by intense pruritus of the dorsal and lateral parts of the underarms and elbows, usually presenting with burning, prickling, or picking sensations. Application of ice packs provides relief; this sign is nearly pathognomic for this condition [182]. Brachioradial pruritus may be attributed to neuropathic conditions such as chronic cervical radiculopathy, cervical spondylosis, and transverse myelitis [7,183–185]. A study in 41 patients with brachioradial pruritus revealed cervical spine changes in all patients: 80.5% of these patients had stenosis of the intervertebral foramen or protrusions of the cervical discs leading to nerve compression [186]. The location of the nerve compression lesions correlated significantly with the dermatomal localization of pruritus: in 90.2% patients marked with C5 location, and in 100% with the C6 location on the dermatom chart [186]. A spinal cord tumor has been reported in a patient with brachioradial pruritus [187]. The occurrence of brachioradial pruritus in several members of one family affecting two generations has also been described [188].

The temporal course of itching in brachioradial pruritus in some patients and the histological changes in the skin, similar to those caused by UV light, indicate that sunlight may be a contributing factor [189]. According to a recent study in 95 patients, 80% had seasonal symptoms [190]. However, radiographic evaluation was only performed in 36 patients. The role of UV light and the histological changes in the skin, similar to those caused by UV light, need to be determined [190].

It is believed that cervical spine disease is the most relevant etiological factor in brachioradial pruritus [190].

In 20 patients suffering from anogenital pruritus without any skin disease or anorectal pathology, lumbosacral radiculopathy and degenerative changes of the lower spine were confirmed in 80% of cases [101].

Postherpetic itch after shingles affecting the head or neck is more likely to occur than after shingles of the torso [176]. Neuropathic itch is more likely to be caused by lesions of the peripheral rather than central neurons. One type of facial neuropathic itch that progresses to scratching-induced ulcers is TTS. Intractable pruritus and profound cutaneous deafferentation makes scratching painless in TTS. The most common brain lesion causing neuropathic itch is cerebral infarction, particularly strokes that affect the lateral medulla or the lateral pons [176]. Small-fiber polyneuropathy (SFPN) is characterized by chronic pruritus of both feet, the feet and legs, the hands and legs, and sometimes also spreading throughout the body. Pain, paresthesias or dysesthesias may be accompanied. Pruritus is fairly common in familial Jakob–Creutzfeldt disease, noted in 19% of patients [191]. Pruritus in multiple sclerosis appears to be rare, rather occurring in early disease stage, but epidemiological data are missing [192]. No epidemiological data are available on post-CVA itch.

**Prognosis**

The prognosis depends on identifying an underlying cause – such as cervical radiculopathy (brachioradial pruritus) and degenerative changes in the vertebrae (notalgia paresthetica) – and on the pathogenicity of the underlying disease (e.g., multiple sclerosis, cerebral infarction).

**Diagnostic tests**

Radiological examinations of the spine, including magnet resonance tomography, should be performed in cases of brachioradial pruritus and notalgia paresthetica as well as magnet resonance tomography of the brain in cases of multiple sclerosis or brain tumors [181,185,186,193]. Further neurological examinations are necessary according to the suspected etiology of pruritus; for example, in SFPN, distal-leg skin biopsy and autonomic function testing.

**Aims of treatment**

Abolition of itching, reducing discomfort, improving the quality of life.

**Relevant outcomes**

Abolition of itch.

**What are the major causes of neuropathic itch?****Are there any effective treatments for it?****Evidence summary: efficacy**

Topical local anesthetics (e.g., polidocanol) are of symptomatic help, but there are no RCTs in neuropathic pruritus.

Topical capsaicin 0.025% four times daily showed significant antipruritic efficacy in a randomized, double-blind, crossover, placebo-controlled 10-week study in 20 patients with notalgia paresthetica. Seventy percent of the patients treated with capsaicin and 30% of those treated with placebo improved [194]. In 24 patients with notalgia paresthetica, relief of up to 90% was achieved in 70% in a noncontrolled, nonrandomized study with topical capsaicin 0.025% four times daily [195].

When 15 patients with brachioradial pruritus were treated with capsaicin 0.025% four times daily for 3 weeks, 10 of 13 patients who completed the study experienced significant or complete relief after 3 weeks in comparison with an untreated arm that served as a control [196].

A systematic review of topical capsaicin in the treatment of pruritus identified two studies concerning treatment of brachioradial pruritus [188,194]. The study on notalgia paresthetica reported a significant difference in the first phase of a crossover study favoring capsaicin over placebo in a visual analogue scale for itch intensity, but failed to report data for a second outcome measure. The final study on brachioradial pruritus reported no significant reduction in itch between capsaicin and placebo [107].

When 16 patients with notalgia paresthetica or brachioradial pruritus were treated with cutaneous field stimulation once daily, 20–30 min a time for 5 weeks in an open trial, pruritus was reduced by 49% at the end of the fifth week in comparison with baseline values [197].

Gabapentin is an anticonvulsant structurally related to the neurotransmitter gamma-aminobutyric acid. The mechanism of action is unclear. Several case reports demonstrated efficacy of gabapentin for brachioradial pruritus. The dosage needed ranged from  $6 \times 100$  mg daily or  $3 \times 300$  mg daily up to  $3\text{--}6 \times 600$  mg daily [198–201]. RCTs are missing.

Oxcarbazepine, a keto-analogue of the anticonvulsant carbamazepine, decreased pruritus when administered to a group of five patients at a dosage of 300 mg twice daily [202].

Fifteen patients with neuropathic scrotal pruritus were treated with paravertebral injections consisting of 2.5 mL triamcinolone and 2.5 mL lidocaine 1% divided into five or six separate injections, with a significant decrease in the mean pruritus scores assessed by the patients before and after therapy [101].

In a retrospective case series, 16 patients with segmental pruritus were treated with deep intramuscular stimulation acupuncture to the paravertebral muscles in the dermatomal segments of the body affected. Twelve patients had complete resolution and four had partial resolution of the pruritus. Relapses occurred in 37% of patients within 1–12 months, requiring further acupuncture. The author described this form of pruritus as “neurogenic pruritus” [203]. Physical therapy including strengthening and stretching exercises have been reported as a reasonable first-line or adjunctive treatment in cases of notalgia paresthetica [204].

#### Key points: neuropathic itch

- Neuropathic itch is an important differential diagnosis in patients suffering from chronic itch.
- Neuropathic itch needs appropriate diagnostic evaluations and neurological assessments.
- Topical capsaicin treatment and systemic gabapentin therapy seem to be effective, but RCTs are missing.

## Pruritus in pregnancy unrelated to skin diseases

### Definition

Pruritus during pregnancy unrelated to skin diseases, especially unrelated to pregnancy-specific dermatoses and without skin lesions, can occur as ICP [205,206]. It may be associated with clinical jaundice. Particularly in the older literature, some authors used the terms “pruritus gravidarum” and “intrahepatic cholestasis of pregnancy.” ICP is the only specific dermatosis of pregnancy that starts solely with itch. Owing to scratching, skin lesions such as papules, nodules, excoriations, and crusts may result later. Some authors have suggested that pruritus gravidarum in women with an atopic predisposition can result in prurigo of pregnancy [207]. According to a newer classification of specific dermatoses of pregnancy, this resembles atopic eruption of pregnancy [205].

### Incidence/prevalence

Epidemiological studies focusing on the prevalence of pruritus during pregnancy unrelated to skin diseases are limited. Interestingly, pruritus is described as the main dermatological symptom during pregnancy and is observed in approximately 18% of pregnancies [208].

A French prospective study of 3192 pregnant women showed that 1.6% had pruritus [209]. Seventeen patients (0.5%) had pruritus gravidarum, while all of the other cases were pregnancy-specific dermatoses [209]. The prevalence of pruritus in pregnancy was reported to be 4.6% in an Indian study of 500 pregnant women, but with the exception of four cases of pruritus gravidarum all of them were suffering from specific dermatosis of pregnancy [210]. The prevalence of pruritus gravidarum was 0.8% [210]. The rate of intrahepatic cholestasis is higher in Chile, related to ethnic and dietary factors. A prevalence rate of 13.2% was found for pruritus gravidarum and 2.4% for cholestatic jaundice of pregnancy [211]. ICP was diagnosed in 3% of pregnant patients in a retrospective two-center study [205].

### Etiology

Pruritus in pregnancy can occur with or without intrahepatic cholestasis. Intrahepatic cholestasis is associated with dyslipidemia, which may contribute to the pathogenesis of intrahepatic cholestasis [212]. The elevation of low-density lipoprotein cholesterol and the reduction of high-density lipoprotein cholesterol may prove to be a useful marker for the early identification of intrahepatic cholestasis of pregnancy and differentiation from pruritus without intrahepatic cholestasis [212]. The cause of the itching in cholestasis, originally thought to be due to bile acids, is now also believed to be due to increase in activity of lysophospholipase autotaxin and its product lysophosphatidic acid [56], also see section on “Pruritus of cholestasis and hepatic disease.”

ICP represents a genetically linked, hormonally induced reversible cholestasis that typically manifests in late pregnancy [205]. Of patients with ICP, 88% reported previously affected pregnancies. ICP is associated with significant fetal risk (premature birth, intra-partal fetal distress, stillbirth), and small-for-date children may be seen [205].

It is estimated that pregnant women take three to eight different medications – some over-the-counter ones, some prescribed by physicians [213]. Drug-induced pruritus during pregnancy is not one of the more probable differential diagnoses, but chloroquine-induced pruritus in malaria therapy during pregnancy is a frequent

cause in tropical regions, with a prevalence of 65%. According to one study, it occurred in 75% of those affected within 24 h after consumption and was described as severe by over 60% of the patients [214].

### Prognosis

In ICP there is a possibility of recurrence during a subsequent pregnancy that can imply an increased risk to the fetus, such as impaired development, intrauterine death, or premature birth [205,210]. One population-based study compared pregnancies in women with and without pruritus gravidarum. Of 159 197 deliveries, 376 (0.2%) occurred in patients with pruritus gravidarum. Using a multivariate analysis, the following conditions were found to be significantly associated with pruritus gravidarum: twin pregnancies, fertility treatments, diabetes mellitus, and nulliparity. No significant differences were noted between the groups with regard to perinatal outcomes, such as birth weight, low Apgar scores, or perinatal mortality. Pruritus gravidarum, associated with multiple gestations, fertility treatments, diabetes mellitus, and nulliparity, is not associated with adverse perinatal outcomes. However, there are higher rates of labor induction and cesarean delivery [215].

### Diagnostic tests

Diagnostic tests include bile acids, transaminases, alkaline phosphatase, cholesterol, and lipids. Measurement of glutathione S-transferase  $\alpha$  (GSTA), a marker of hepatocellular integrity, provides a test of liver dysfunction that distinguishes between pruritus gravidarum with and without intrahepatic cholestasis [216]. Levels of autotaxin and lysophospholipase autotaxin may be utilized as markers of ICP [56].

### Aims of treatment

Abolition of itching, reducing discomfort, improving the quality of life.

### Relevant outcomes

Abolition of itch.

### What are the major causes of pruritus during pregnancy unrelated to skin diseases? Are there any effective treatments?

#### Evidence summary: efficacy

Aspirin showed significant antipruritic efficacy in a systematic review when it was administered at a dosage of 600 mg four times daily in comparison with chlorpheniramine 4 mg three times daily applied during late pregnancy. Aspirin was more effective in relieving itch, but chlorpheniramine was more effective than aspirin when a rash was present [217]. Aspirin may not be given during the last trimester, as it can lead to early occlusion of the ductus arteriosus.

There are no studies on the efficacy of antihistamines for the treatment of pruritus during pregnancy, but there are studies concerning their safety. The older sedating antihistamines, such as chlorpheniramine, dimetindene, diphenhydramine, and hydroxyzine, are considered relatively safe during pregnancy, on the basis of long-term experience and several independent animal studies, and these agents have not shown any teratogenic effects [213]. In animal studies during pregnancy, astemizole, terfenadine, and cetirizine did not show any notable effects in influencing the fetus, but terfenadine and fexofenadine led to decreased fetal weight gain. In younger generation antihistamines (e.g., levocetirizine), animal

studies so far have not demonstrated any impairment of pregnancy or of embryonic and fetal development. Second- and third-generation antihistamines should not be administered during the first trimester of pregnancy. If antihistamines are necessary during this period of pregnancy, the older sedating ones are preferable. Fexofenadine, terfenadine, and astemizole are not suitable for treatment during pregnancy [213].

There have been no studies investigating the efficacy of glucocorticosteroids in patients with pruritus during pregnancy.

Cholestyramine binds bile acids. According to uncontrolled studies, it may be effective in up to 70% of patients suffering from ICP [206,207]. Ursodesoxycholic acid enhances the excretion of bile acids. It is very effective when administered at daily doses of between 450 and 1200 mg, as shown in four small controlled trials [207]. Others recommend 15 mg/kg per day or 1 g, either per day or distributed over several days [206]. In ICP, therapy with ursodesoxycholic acid should start as soon as possible as it relieves itch, but especially improves fetal prognosis [206].

The administration of UV therapy during pregnancy is not generally contraindicated, but it should be carried out with caution and should be performed when skin lesions are present. It should be limited to late pregnancy and should be performed only after the patient has been provided with thorough information. PUVA therapy with oral psoralen administration is contraindicated.

#### Key points: pruritus in pregnancy

- Pruritus during pregnancy without any skin lesions usually presents as ICP.
- The prevalence of pruritus during pregnancy shows substantial geographical variation.
- There are too few controlled studies investigating treatment for pruritus during pregnancy for conclusions to be drawn.

## Pruritus of unknown origin

### Definition

Itching without any underlying etiology after thorough history-taking and examination of the skin and general examination [21] is termed pruritus of unknown or undetermined [1] etiology. Some authors also use the terms “idiopathic pruritus” and “idiopathic itch.” Pruritus of unknown origin is rare in children but more common in adults, especially the elderly. This type of pruritus is characterized by prolonged persistence, lasting months to years.

### Incidence/prevalence

There are limited epidemiological data on the incidence and prevalence of pruritus of unknown origin. In 132 German patients suffering from pruritus as a leading symptom, it was impossible to identify an underlying etiology in 8% [4]. In 3/84 Ugandan patients (3.6%), the cause of chronic itch was unknown [4]. A study investigating outpatients presenting with pruritus of unknown origin identified an underlying systemic disease in 11 of 50 patients. The cause of itch was unknown in 13/43 (30%) cases of generalized itch [218]. In 34 inpatients admitted for investigation of treatment of generalized itch, three had no etiological factors (8.8%) [219].

Analyzing 74 problem cases of itching revealed 10 unexplained cases (13.5%) [220]. In a German retrospective study of underlying diseases in 263 patients with chronic itch, no disease was found in 44.5% of patients; 55.6% of them, especially elderly patients, had many cofactors contributing to chronic itch, suggesting its multifactorial origin [221].

### Prognosis

According to one clinical study, the prognosis is poorer and the quality of life is significantly more impaired in idiopathic pruritus in comparison with pruritus in dermatological and systemic diseases [4]. A study in 75 patients with pruritus of unknown origin found that 55% of patients reported to be more agitated and 23% were depressed, and 15 (20%) were anxious [222].

### Aims of treatment

Abolition of itching, reducing discomfort, improving the quality of life.

### Relevant outcomes

Abolition of itch.

### Have any effective therapies been reported for pruritus of unknown origin?

#### Evidence summary

Sixty patients with “idiopathic perianal pruritus” were treated either with topical steroids twice daily (methylprednisolone) for 2 weeks ( $n = 28$ ) or with a liquid cleanser twice daily for 2 weeks ( $n = 32$ ). Treatment was effective in 93% of the patients receiving topical steroid treatment and in 91% of those treated with the liquid cleanser. There were no significant differences between the two treatments, suggesting that perianal cleansing is as effective as topical corticosteroids [116]. Fifteen patients with idiopathic anogenital pruritus were treated with paravertebral injections consisting of 2.5 mL triamcinolone and 2.5 mL lidocaine 1% divided into five or six separate injections, with a significant decrease in the mean pruritus scores assessed by the patients before and after treatment [101].

There have been no studies on UV phototherapy in patients with pruritus of unknown origin. UVB or a combination of UVA–UVB phototherapy can be tried, depending on the status of the skin (e.g., UV-light sensitivity, itching of the whole body).

Also, in pruritus of unknown origin, general itch-relieving measures should be applied; for example, avoiding of dryness of the skin, skin moisturizing on a daily basis, use of symptomatic itch-relieving topicals such as polidocanol and menthol. In cases of localized itch, topical immunomodulators and topical capsaicin may be tried. According to recent studies and the European guideline on chronic pruritus, the following therapies may be tried in pruritus of unknown origin: desloratadine up to  $3 \times 10$  mg/day, naltrexone 50–150 mg/day, gabapentin  $3 \times 100$  mg/day to  $3 \times 900$  mg/day, paroxetine 20–40 mg/day [21].

#### Key points: pruritus of unknown origin

- Pruritus of unknown origin has a major impact on a patient's quality of life and mood. Therapy is a challenge in this group of patients, as no effective treatments are available. The available data are insufficient for conclusions to be drawn.

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# Vulval lichen sclerosus, erosive lichen planus, and vulvodynia

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## Background

Vulval skin conditions have long been a neglected area of research in medicine, resulting in the absence of even basic data such as estimates of disease prevalence. Additionally, it is common for affected individuals to delay seeking medical advice through fear and embarrassment. Finally, through lack of training [1] the medical profession will often fail to fully explore vulval symptoms; women may present to a range of different specialities, and making the correct diagnosis may take considerable time.

Survey-based studies indicate that vulval skin disorders are much more prevalent than once thought. In a survey of 79 UK general practitioners, over half saw more than three patients with vulval disorders per month [2] and a US-based community survey of 303 women reported 18.5% having lower genital tract discomfort lasting longer than 3 months [3].

Vulval skin complaints are important as they cause considerable distress and can affect both physical and psychological well-being [4, 5]. Furthermore, certain inflammatory vulval conditions have potential for progression to malignancy.

Although there are numerous conditions that could be addressed in this chapter, three important disorders that are managed frequently within the vulval speciality clinic have been selected and the evidence for their treatment reviewed.

## Lichen sclerosus

### Definition

Lichen sclerosus (LS) is an inflammatory dermatosis predominantly affecting the anogenital skin in both sexes. It is intensely itchy, often keeping people awake at night, and scratching results in painful fissures. In children, perianal fissures often present as constipation.

Clinical features are usually diagnostic as white papules, plaques and hemorrhage occur in a “figure of eight” distribution around the periclitoral and perianal regions. There is “cigarette paper” thinning of affected skin which will frequently break, resulting in fissures, often in the interlabial sulci. Hyperkeratosis may occur in other

areas. LS only affects keratinized squamous epithelium and, therefore, spares the vagina.

Whilst LS may affect males as well as females, for the purpose of this review the data have only been presented in the context of vulval disease.

### Incidence/prevalence

The true incidence of LS is unknown, although it is the most frequent dermatosis managed in vulval specialist outpatient clinics. Figures between 1/300 and 1/1000 [6] women have been made, but this is likely to be an underestimate. There are two recognized peaks of presentation: one in the prepubertal years and the other in the postmenopausal years [7, 8]. Although childhood LS usually improves, there may be cases that persist into adulthood, and young patients should be managed with this in mind [9].

### Etiology

The pathogenesis of LS is not truly understood. However, autoimmunity is thought to play a part and, in keeping with other autoimmune disorders, LS occurs more frequently in females. It is also associated with other autoimmune disorders [10], particularly thyroid disease [11]. A large observational cohort study of 1000 vulval LS patients showed that 12% had a positive family history of LS, suggesting a genetic or familial clustering effect [12].

### Prognosis

In general, LS responds well to treatment and most women will experience good disease control with improvement of signs and symptoms. Reduction in itch is usually the first symptom to be reported. The clinician will see loss of hemorrhage, reduction in hyperkeratosis, and healing of fissures, although pallor may persist. It should be possible in most cases to avoid scarring, which can result in dyspareunia and difficulty in micturition. Hyperkeratotic variants of LS are particularly associated with squamous cell carcinoma with an estimated risk between 2 and 5% [8, 13]. It is unclear whether better disease control reduces the risk of malignant transformation.

## Diagnostic tests

The diagnosis of LS can usually be made clinically. Guidelines issued by the British Association of Dermatologists for the management of LS suggest that a confirmatory biopsy is ideal, although not always practical [14]; for example, in children, or when disease affects sensitive anatomical areas, such as the clitoris. Histological examination should be made in cases with atypical features if there is diagnostic uncertainty or suspicion of neoplastic change, such as unresponsive disease hyperkeratosis or nonhealing ulceration [14].

## Aims of treatment

Affected individuals should be reassured that, with adequate early treatment, LS can be well controlled with full remission of symptoms and restoration of normal sexual function. The overall aims of treatment are:

- 1 reduction in disease morbidity by reducing itch, pain, and constipation;
- 2 prevention of scarring and maintenance of normal architecture with preservation/restoration of usual sexual function;
- 3 reduction of hyperkeratosis and risk of malignant progression.

## Relevant outcomes

As there are no outcome measure scales specific to vulval skin disease or LS [15], the outcome measures used are those involving a patient-rated change in symptoms and a clinician-rated change in appearance. Specific patient-rated considerations relate to itch, pain, and sexual function. Clinician-directed assessment is reduction in hemorrhage, pallor, and hyperkeratosis.

## Search methods

Medline, Embase and the Cochrane Database of Systematic Reviews/Cochrane Central Register of Controlled Trials were searched from the time of inception up to July 2012. Searches used the MeSH terms “Lichen sclerosus et atrophicus” and “vulvar lichen sclerosus” in combination with the Cochrane collaboration’s filter method for randomized controlled trials (RCTs).

## Questions

### Case scenario 72.1

A 59-year-old female presented with a 6-month history of intractable vulval and perianal itch. On examination there was pallor and hyperkeratosis in a “figure of eight” configuration involving the periclitoral and perianal skin (Figure 72.1). A diagnosis of LS was made.

### What is the evidence for topical treatments in adult vulval lichen sclerosus?

The usual clinical practice for the treatment of LS in adults is to use superpotent topical corticosteroids. There is an emerging literature for the use of topical calcineurin inhibitors. Evidence for the use of topical therapy in LS is considered and the best quality RCTs are described below.

#### Efficacy

##### Topical corticosteroids

A Cochrane systematic review of topical interventions for LS [16] affecting the genital region found some limited RCT evidence for the treatment of LS with topical corticosteroids. In total there was only one study included in the review comparing topical corticos-



**Figure 72.1** LS in a postmenopausal woman showing the classical figure of eight distribution and fissuring in the peri clitoral region.

teroids against placebo, to control the disease in females [17]. In this study, Bracco *et al.* randomized 79 patients with biopsy-proven LS to receive clobetasol propionate, topical testosterone, topical progesterone, or placebo.

Topical clobetasol propionate was used in 20 patients for 3 months against 19 patients in the control group, who received a cream-based placebo. Clobetasol propionate was significantly better than placebo in relation to the following outcomes: “participant-rated improvement or remission of symptoms” (risk ratio [RR], 2.85; 95% confidence interval [CI], 1.45–5.61) and “investigator-rated global degree of improvement” (standard mean difference [SMD], 5.74; 95% CI, 4.26–7.23).

##### Topical hormone preparations

Historically, the role of topical testosterone has been considered as a treatment option for controlling LS. In the same study just described, Bracco *et al.* [17] found that 3 months’ application of testosterone was significantly less effective than clobetasol propionate with regard to participant-rated improvement or remission of symptoms (RR, 0.67; 95% CI, 0.45–0.98) and investigator-rated global degree of improvement (SMD, –1.81; 95% CI, –2.56 to –1.06). No significant differences in adverse drug reactions were found between the testosterone and clobetasol propionate groups.

Topical progesterone 2% was compared against placebo in the study by Bracco *et al.* [17] and was found not to be significantly better for patient- (RR, 1.58; 95% CI, 0.72–3.50) or clinician-related outcomes (SMD, 0.34; 95% CI, –0.29 to +0.97).

In another study, Sideri *et al.* [18] found no significant difference between topical testosterone 2% compared with placebo in 58 women with histologically confirmed LS treated over 1 year.

##### Topical immunomodulators?

There has been one RCT study testing the efficacy and safety of pimecrolimus (1% cream) against clobetasol propionate 0.05% after 12 weeks’ application [19]. Both agents were effective in relieving

pruritis (SMD,  $-0.33$ ; 95% CI,  $-0.99$  to  $+0.33$ ) and burning/pain (SMD,  $0.03$ ; 95% CI,  $-0.62$  to  $+0.69$ ), and there were no significant differences between the two. However, when assessed by the “Investigator-rated global degree of improvement,” pimecrolimus was less effective than clobetasol propionate (SMD,  $-1.64$ ; 95% CI,  $-2.40$  to  $-0.87$ ). There were no adverse drug reactions reported in either group.

There have been no RCTs to date assessing the efficacy of topical tacrolimus in the treatment of vulval LS; however, a case series of 84 patients (49 women, 32 men, and three girls) has supported the efficacy of tacrolimus [20].

### Drawbacks

In both of the RCTs reported [17, 19], both clobetasol propionate and pimecrolimus appeared to be well tolerated with no adverse effects (e.g., predisposition to infection, worsening of skin atrophy, and contact dermatitis) reported.

However, the long-term safety profile of calcineurin inhibitors is not established, and there are concerns about an increased risk of neoplasia with their use in a disease with a pre-malignant potential [21–23]. There are case reports of squamous cell carcinoma developing in patients who have been using these treatments [24, 25], and their long-term use in LS is currently not advised.

### Comment/implications for clinical practice

Trial data about the treatment of LS in adults are still limited, but it would appear that a superpotent corticosteroid (clobetasol propionate 0.05%) should be first-line therapy [17]. There are no RCT trial data for the optimum frequency of application or duration of the steroids; and even the RCTs included different frequency of use of topical steroids: clobetasol propionate 0.05% was applied twice daily for 1 month then once daily for 2 months in the Braco study [17], whereas in the Goldstein trial comparing pimecrolimus and clobetasol propionate [19], clobetasol propionate was applied once daily.

The British Association of Dermatology Guidelines [14] suggest application once daily, at night, for 4 weeks, then on alternate nights for 4 weeks, and then twice weekly for a further 4 weeks, before review. The rationale for once-a-day application is based on pharmacodynamic studies showing that an ultrapotent steroid only needs to be applied once a day on extragenital skin [26]. If symptoms recur when the frequency of application is reduced, the patient is instructed to use the treatment more often until the symptoms resolve. They can then try to reduce the frequency again. A 30g tube of clobetasol propionate 0.05% should last at least 12 weeks [14]. In steroid-resistant disease or cases where there is contact dermatitis, the evidence suggests that calcineurin inhibitors such as pimecrolimus might be efficient and well tolerated [19], but should be used with caution on a short-term basis where possible.

### Case scenario 72.2

A 9-year-old girl presents with a 6-month history of observed rubbing in the genital region. She has also become more constipated with pain on defecation. Clinical findings were in keeping with lichen sclerosus and are shown in Figure 72.2.

### What is the evidence for treating lichen sclerosus affecting children with topical steroids?

#### Efficacy

Whilst in adults it is accepted that superpotent topical steroids should be the first-line choice, there are no ongoing RCTs to base



Figure 72.2 LS in a prepubertal female.

this recommendation in childhood LS. In a case of 70 cases of childhood vulval LS, potent topical corticosteroids were effective treatment to alleviate symptoms, without significant side effects [27]. This has also been reported in two other smaller studies [28, 29].

A small study on the use of pimecrolimus in four prepubertal girls also noted an improvement in symptoms [30]. However, stinging on application was often reported.

### Drawbacks

There are only limited data for the treatment of LS in children with potent topical steroids and calcineurin inhibitors. The use of calcineurin inhibitors was associated with stinging [29]. As with the adult population, there is also the concern that long-term treatment with these drugs could be associated with neoplastic change.

### Comment/implications for clinical practice

The evidence for the use of topical steroids in children is limited. Through the case series evidence available, it would appear that potent topical steroids are effective in the alleviation of the symptoms of LS without obvious side effects [27, 28]. The use of pimecrolimus is also reported, but this is a very small case series of only four girls [30].

## Erosive lichen planus

### Definition

The erosive subtype of lichen planus (ELP) is a chronic, inflammatory disorder that may affect any surface lined with squamous epithelium. In contrast to the non-erosive subtype, which affects mainly the skin, typical areas of involvement include the mucosal surfaces of the oral and genital regions. Of particular note is the “vulvo-vaginal gingival syndrome,” an uncommon, but severe variant concomitantly affecting the vulva, vagina, and gingiva.



## Incidence/prevalence

The true incidence and prevalence of genital ELP is unknown. Studies of patients attending vulval specialty clinics have found that vulval ELP accounted for 3% [31], 5.9% [32], and 8% [33] of all new referrals. In a case series of 3350 vulval biopsies, the prevalence of vulval ELP was 3.7% [34]. These figures indicate that vulval ELP is not so rare as once thought, although this is still likely to be an underestimate of the overall problem.

## Etiology

Current thinking is that autoimmune mechanisms cause basement membrane zone (BMZ) disruption and that vulval ELP is an autoimmune condition [35]. An increased prevalence of autoimmune disorders has been demonstrated in patients with vulval ELP [10], and circulating autoantibodies targeted towards specific BMZ proteins (BP 180) have been located [36]. However, it is not clear if these antibodies are directly pathogenic, or whether they are a result of epitope spread due to BMZ damage from another cause.

## Prognosis

Unlike classical (non-erosive) LP, which is self-limiting and responds well to therapy, vulval ELP takes a relapsing–remitting, chronic course and is often treatment resistant. Scarring is common and causes anatomical destruction with loss of function (such as micturition and sexual activity). Vulval ELP is thought to have malignant potential, with an estimated 3% of cases developing squamous cell carcinoma [37].

## Diagnostic tests

The diagnosis of vulval ELP is made clinically with appropriate histopathological correlation. This is largely due to the nonspecific histological features found on biopsy and the differential diagnosis of erosive lesions in the vulval region, including intraepithelial neoplasia and bullous disease [6, 38, 39]. Typical clinical findings include well-demarcated introital erosions/erythematous areas (plus/minus hyperkeratotic white edge), which may be seen in combination with similar vaginal lesions. There may also be evidence of scarring with loss of the labia minora, as well as evidence of other affected sites, such as the oral cavity.

Histopathological findings are variable and around 25% will show nonspecific features, especially if taken from eroded areas. The most characteristic lichenoid changes are found when a biopsy is taken from the edge of the lesion, particularly at a hyperkeratotic white margin [40]. It is important to consider secondary infection or associated autoimmune disease when there is a poor response to therapy, and biopsy should be performed in atypical cases or where there is diagnostic doubt.

## Aims of treatment

Treatment aims are:

- 1 reduction in disease morbidity through improving symptoms (mainly pain);
- 2 prevention of scarring and maintenance of normal architecture with preservation/restoration of usual sexual function;
- 3 reduce the risk and monitor for signs of malignant progression.

## Relevant outcomes

Affected individuals are clinically assessed for disease impact and severity, but the therapeutic ladder is driven by the patient response to therapy and how they report their symptoms [41]. As such,

outcomes important in clinical practice are mainly *patient-oriented* and include reduction of symptoms and improvement in health-related quality of life (HRQoL). Clinical outcomes are assessed by the clinician and include the reductions of erythema, erosions, and pain on Q-tip pressure. Currently, there are no vulval or ELP-specific outcome measure scales available [15].

## Methods of search

Medline, Embase and the Cochrane Database of Systematic Reviews/Cochrane Central Register of Controlled Trials were searched from the time of inception up to June 2012, using the key terms “vulva” and “lichen planus”. Because of the lack of controlled studies in this area, evidence from open studies and case series were also reviewed.

## Questions

### Case scenario 72.3

A 58-year-old female presents with a 3-month history of vulval soreness and pain on sexual intercourse. Self-medication with topical antifungal agents had been unsuccessful. Examination revealed well-demarcated introital erosions with a hyperkeratotic white border (Figure 72.3).

### What is the evidence for topical treatments in vulval erosive lichen planus?

Usual clinical practice for the treatment of vulval ELP is to use superpotent topical corticosteroids [42]. There is an emerging literature for the use of calcineurin inhibitors [43–45]. The evidence for the use of topical therapy is considered below.

## Efficacy

### Topical corticosteroids

In general, there is a lack of good-quality trial data for ELP. A Cochrane systematic review of interventions for ELP affecting mucosal sites [46] found no RCT evidence for vulval ELP. Of 15 studies which were included in the Cochrane review, all were for *oral* ELP. There was no overwhelming evidence for the efficacy of a single treatment in the oral subgroup, including topical steroids, which are the current accepted first-line therapy.



**Figure 72.3** Well-demarcated vulval introital erosions with a hyperkeratotic white border.



A subsequent systematic review and meta-analysis of treatments for LP (both cutaneous and mucosal subsets) [47] has been reported in a conference abstract. Of the 54 identified RCTs involving mucosal LP, only one was for vulval disease; the rest were in patients with oral disease. The authors commented upon a lack of clear and accurate measurements of disease outcome or severity. They were unable to perform a meta-analysis of RCTs for mucosal LP, although they did comment that, from the meta-analyses included in their review, the potent topical corticosteroids betamethasone valerate and fluocinolone are more beneficial than placebo for *oral* ELP. However, no figures were given to back up this claim, and as this is a conference abstract with limited information it has not been possible to appraise the methods used for the search.

Only one *prospective* case series documenting response to topical corticosteroids was found. Cooper *et al.* [37] followed 114 adult women with definite clinical diagnosis of ELP of the vulva for a mean duration of 72 months. Within this group, the most frequent first-line therapy given was clobetasol propionate 0.05% ( $n = 89$ ): 84/89 showed symptomatic improvement and 63/89 became symptom-free during treatment. Interestingly, symptomatic improvement did not correlate with clinical improvement and, overall, only 10/114 patients had complete resolution of clinical signs with treatment. Other *retrospective* case-series have shown *partial* response to superpotent topical steroids [48, 49].

#### Topical immunomodulators?

One *prospective* case series has specifically looked at the effects of topical pimecrolimus in 11 women who had not responded to topical corticosteroids [45]. Following twice-daily application of pimecrolimus for 4–6 weeks, 2/11 showed complete resolution of symptoms and 7/11 showed partial response. Pimecrolimus was found intolerable in 2/11.

There were seven patients treated with topical tacrolimus and one with topical pimecrolimus in the case series reported by Cooper *et al.* [37]. Response was reported as “good” in two, “partial” in four, and “poor” in two of these patients.

Other *retrospective* case series have reported a mixed response to topical immunomodulators [32, 44]. In a retrospective review of the use of topical tacrolimus in patients with vulval ELP who had “recalcitrant” disease and had failed at least topical corticosteroids (potency unclear), 15/16 patients were “much” or “somewhat” better after twice-daily application for 3 months [44]. In contrast, Helgesen *et al.* [32] only reported complete response in 3/22 and partial response in 6/22 patients to topical tacrolimus. The remaining 13 showed no response. It is not clear which prior treatments patients had received or how long their therapy was given in this study.

#### Intravaginal steroid enemas?

A single-center, nonrandomized, retrospective cohort study assessed the effects of hydrocortisone 25 mg suppositories b.i.d. (subsequently tapered off to achieve a symptom-free maintenance dose) in 60 patients with *vaginal* ELP [50]. Complete response data were only available for 43 patients. Overall symptomatic improvement as reported by the patients was as follows: 58.1% improved; 23.3% “somewhat” improved; 16.3% were unchanged; and 2.3% were worse.

#### Other topical treatments

In the *only* RCT identified by the literature search, *Aloe vera* gel was compared against placebo in 34 women with vulval ELP [51]. It was

reported that 14/17 (82%) of patients showed complete or good response to *Aloe vera* gel compared with 1/17 (5%) in the placebo group ( $P < 0.001$ ). However, this was a poorly reported study and a number of key factors were not clear, such as the method of randomization, concealment of allocation, or baseline characteristics in each of the groups. Furthermore, there was no intention-to-treat analysis, no flow diagram of participants, and the outcome measures used was a score designed for *oral* ELP (the “Thongprasom score”).

#### Case scenario 72.4

A 63-year-old female presented with a 2-year history of ELP affecting the oral and genital mucosa. Response to topical therapy had been poor. She had evidence of genital scarring with loss of the labia minora and introital narrowing (Figure 72.4). She reported ongoing vulval pain and burning, leading to a loss of sexual function.

#### In erosive lichen planus affecting the vulva that is unresponsive to topical treatment, what is the evidence for systemic treatment?

##### Efficacy

The only evidence found describing the effects of systemic therapy in ELPV were case series and case reports. The case series with the largest number of patients was by Hubbard *et al.*, who document the effects of hydroxychloroquine [52] in 17 patients. A 12-month course of hydroxychloroquine was completed by 15 patients, 13 of whom showed “good” symptomatic improvement. These results were reported in a conference abstract, and outcomes were measured by a “severity” index devised by the authors.

Pelisse [40] reported a good response to oral prednisolone in 10 patients with the vulvo-vaginal gingival syndrome.

Numerous other systemic therapies have been reported upon, either as single case reports or as part of a larger case series.



**Figure 72.4** Advanced ELP with scarring causing loss of normal architecture. Well-demarcated erythematous erosions are present.

However, numbers were all in single figures, and conclusions cannot be drawn from these articles. In their prospective case series, Cooper *et al.* [37] comment that “systemic treatments were surprisingly unhelpful, with a uniformly poor response to systemic immunosuppressants”; however, prednisolone, ciclosporin, and azathioprine had only been given to three, two, and one patient, respectively.

## How effective is surgical intervention to treat scarring?

### Efficacy

Again, only retrospective case series and case reports were available. The largest number of patients were documented by Helgesen *et al.* [32], who reported “good” response in 13/17 patients who underwent dilatation procedures in conjunction with topical steroids. However, relief was to a varying degree, often with some recurrence.

### Drawbacks

Adverse events were not commonly reported in the studies reviewed. Byrd *et al.* reported irritation from topical tacrolimus in 6/16 patients [44], and from Lonsdale-Eccles and Velangi’s case series [45] 2/11 patients (18%) were unable to tolerate pimecrolimus owing to local irritation. Topical immunomodulators have received attention for their theoretical potential to cause infection or contribute to the development of malignancy, although no good evidence to support this in vulval skin was found.

### Comment/implications for clinical practice

The most widely accepted first-line therapy for vulval ELP is superpotent topical steroids. However, as demonstrated by the Cochrane review, there is no RCT evidence to support this, or any other treatment modality in the management of the disease. Although the other systematic review identified two potent topical steroids were effective for oral ELP, data for this were lacking as it was a conference abstract. Both reviews commented upon the lack of validated and standardized outcome measures for mucosal ELP.

The case series identified were mainly retrospective. Diagnostic criteria for inclusion of participants and outcome measures used varied widely and were not validated in any way. It is difficult, therefore, to compare datasets, particularly as the method of reporting outcomes was so different. The most comprehensive case series to date [37] indicates that superpotent topical steroids are an effective first-line therapy in around 70% of patients. In the absence of any other evidence, it is reasonable to believe that these should be used as first-line therapy in clinical practice.

The evidence for second-line therapy is severely lacking, even through case series. Responses to treatment with anti-inflammatory and immunosuppressant agents are therefore given on an anecdotal basis at present, and there is an urgent need for controlled trials in this area. Since vulval ELP is a chronic disease, any clinician prescribing systemic therapy should balance the risk of long-term disease control against the potential side effects of the use of the drug.

## Vulvodynia

### Definition

Vulvodynia has been defined by the International Society for the Study of Vulval diseases as vulval discomfort, most often described

as a burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder [53]. The pain of vulvodynia may be localized or generalized, and spontaneous or provoked by touch or pressure on the vulva; for example, during the insertion of sanitary protection, sexual intercourse, or even on wearing clothes. Vulvodynia is a neuropathic pain condition, and on examination there is no evidence of a dermatological problem. The term “vestibulodynia” describes provoked pain localized to the vestibule region, with pain experienced on sexual and nonsexual touch. Clinically, this can be demonstrated using a cotton-tipped swab when applying gentle pressure to the vestibule area. The maximal area of tenderness is experienced over the entrance to the Bartholin’s glands [54]. Some patients may have a combination of vulvodynia with another vulval problem (e.g., herpes or thrush), and both conditions may require treatment. As the condition is frequently chronic, a high level of psychological morbidity is common. Some patients are prone to stress and anxiety, which may play a role in developing symptoms [55]. Sexual dysfunction is common and frequently reported [56]. Reduced sexual arousal, more negative sexual feelings, and less spontaneous interest in sex (not elicited by a partner) have all been described in vestibulodynia [57]. These are all risk factors for significant psychosexual dysfunction, such as vaginismus and anorgasmia, the management of which usually requires psychosexual input.

### Incidence/prevalence

The incidence in the UK remains unknown. However, the prevalence of vestibulodynia was 1.3% of women attending a central London genitourinary medicine clinic [58]. It is likely that patients are misdiagnosed.

### Etiology

This remains unknown, but is likely to be multifactorial. It is often difficult to identify a cause, as symptoms usually develop insidiously. Recurrent attacks of vulvovaginal candidiasis have been suggested as a cause [59].

### Prognosis

Up to 30% of women with vestibulodynia may experience resolution of their symptoms without treatment, and in 50% of these resolution can occur within 12 months [60]. The prognosis for unprovoked vulvodynia remains unclear.

### Diagnostic tests

Vulvodynia is diagnosed clinically without the need for diagnostic skin biopsies. It remains important to ensure that dermatological conditions of the vulva are excluded before making such a diagnosis of vulvodynia. In a paper by Bowen *et al.* [61], 61% of patients with “vulvodynia” actually had a relevant dermatological condition of the vulva and were rediagnosed after a biopsy.

### Aims of treatment

Treatment aims are:

- 1 reduction in pain, improved function;
- 2 if appropriate, increase satisfactory pain-free sexual intercourse.

### Relevant outcomes

Affected individuals are clinically assessed for the severity and level of pain and its impact on function. The therapeutic ladder is driven by the patient response to therapy from a pain and/or psychosexual

perspective. As such, outcomes important in clinical practice are mainly *patient-oriented* and include reduction of symptoms and improvement in HRQoL. A variety of pain management scores are available, such as the Brief Pain Inventory.

### Methods of search

Medline, Embase, and the Cochrane Database of Systematic Reviews/Cochrane Central Register of Controlled Trials were searched from the time of inception up to June 2012, using the key terms “vulvodynia” and “vulval pain syndromes.” Because of the lack of controlled studies in this area, evidence from open studies and case series were also reviewed.

## Questions

### Case scenario 72.5

A 28-year-old female presents with a 9-month history of localized provoked vulval pain. Pain was experienced with tampon use and during cervical smear taking. Examination of the vulva was normal, but there was sensitivity over the vestibule area when touched with a cotton bud.

### What is the evidence for treatments in localized provoked vulvodynia (vestibulodynia)?

A body of evidence now suggests that the management of patients with vestibulodynia is to desensitize the vulval area, as sexual pain is the main complaint. Many women will have secondary vaginismus (involuntary contraction of the pelvic floor muscle) in response to the touch sensitivity (allodynia).

### How effective is psychological and psychosexual therapy in the management of vestibulodynia?

#### Efficacy

Patients with provoked pain (vestibulodynia) may benefit from a psychological approach initially. In one RCT, 78 women with provoked pain were randomized to one of three arms: group cognitive behavioral therapy (for 12 weeks), pelvic floor biofeedback (for 12 weeks), and vestibulectomy [62]. At 6-months' follow-up, all patients reported improvements in pain scores, although there was no significant difference between groups. The study supported both forms of nonsurgical treatment and suggested that patients prefer a behavioral approach to treatment than a surgical one.

### How effective is physical therapy in the management of vestibulodynia?

#### Efficacy

Physical therapy techniques are first-line treatments used to desensitize the vulva. They help reverse an apparent hypertonicity in the levator ani (pelvic floor muscles) and help patients overcome a phobia of genital touch. A variety of physical therapies have been reported to show benefit, including pelvic floor muscle biofeedback, self-massage of the vulva, vaginal transcutaneous electrical nerve stimulation, and the use of vaginal trainers [63–65]. No studies have reported an optimal technique, and success depends on several factors, including the therapist, degree of patient support, and duration and number of sessions. Biofeedback therapy has been used successfully to help overcome pelvic floor muscle dysfunction in women with provoked vulvodynia, with response rates of 52% [63].

### How effective are intralesional injections in the management of vestibulodynia?

#### Efficacy

There is some evidence that intralesional injections into the vulva may be of benefit in patients with provoked vulvodynia, and various drugs have been suggested. Murina *et al.* [66] gave subcutaneous injections of 40 mg methylprednisolone acetate and 10 mg of lidocaine hydrochloride in 10 mL of normal saline into the vestibule in 22 women with vestibulodynia. Follow-up was for a period up to 2 years. In their results they state that 15 women (68%) responded “favorably” to the treatment and 32% experienced complete remission, which occurred about 15 days after treatment. It is worth noting that these favorable results are comparable with those achieved with less invasive, and less time-consuming (for the patients) options. Similar positive results were obtained in trials looking at betamethasone and lidocaine infiltration [67, 68].

### Case scenario 72.6

A 60-year-old female presented with a 4-year history of unprovoked vulval burning and soreness. Her discomfort restricted her socially and she had tried a variety of topical medications without success. Clinical examination of the vulva was normal.

Patients with unprovoked vulval pain are akin to other patients with neuropathic pain and should be managed along similar lines. Sexual pain is less of a problem in this group, and chronic pain management to focus on a reduction in the severity of the pain is a key issue.

### How effective are pain-modifying drugs in the management of unprovoked vulvodynia?

#### Efficacy

There are no RCTs to demonstrate the optimal pain-modifying drug for unprovoked pain. Tricyclic antidepressants, gabapentin, and pregabalin have shown benefit in the treatment of unprovoked vulvodynia in some small cohort studies [69–71]. Complete responses at 6 months of 47% have been reported [72].

It should be noted that, for patients with provoked vulvodynia, the benefit of drugs such as tricyclic antidepressants and gabapentin is less clear, and these would not be considered first-line treatment.

### How effective are topical anesthetics in the management of unprovoked vulvodynia?

#### Efficacy

Topical local anesthetics, such as 5% lidocaine gel or ointment, are commonly prescribed for women with vulvodynia. One RCT found a 33% response rate for placebo compared with 20% for topical lidocaine in women with vestibulodynia, but this was not significant [73]. In addition, local anesthetics are potent sensitizers and should be used with caution on the vulva because they can lead to allergic contact dermatitis.

### Drawbacks

With the exception of the trial by Foster *et al.* [73], all studies lack a placebo-controlled arm and there is a clear need for RCTs focusing on specific subgroups of women with vulvodynia and clear outcomes. Most of the studies are small with inadequate follow-up duration. In addition, treatments are often given in isolation and would be best used in combination.

### Comment/implications for clinical practice

The optimal treatment package is a multidisciplinary approach with the clinician assessing the patient, making a diagnosis, and starting



basic management. Referral to other health professionals (e.g., for psychosexual counseling, pain management, and physiotherapy) may be necessary depending on the individual needs of the patient. Recently, the British Society for the Study of Vulval Diseases published evidence-based guidance on the management of women with vulvodynia recommending this multidisciplinary approach [74]. As dermatologists are seeing patients at the initial referral, it may be appropriate for them to triage these patients and remain as a “lead” for those patients who might need to see two or three different health professionals to address the different aspects of the patient’s complaint. Patients frequently complain that their care is disjointed, and a lead clinician to coordinate care is helpful.

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## CHAPTER 73

# Venous ulcers

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### Background

#### Definition

Venous ulcers are wounds that usually occur in a gaiter distribution of the lower leg (Figure 73.1). They are associated with increased pressure in the superficial venous system of the lower legs during ambulation (ambulatory venous hypertension) and are possibly related to several pathophysiologic mechanisms including failure of the calf muscle pump to return venous flow effectively [1], dysfunction of valves in the superficial and/or communicating veins, dysfunction of valves in the deep venous system, and/or deep venous outflow obstruction [2–4].

#### Incidence/prevalence

Venous leg ulcers are common with an incidence in people over 65 years of age in the UK of 0.76 (95% confidence interval [CI], 0.71–0.83) per 100 person-years for men and 1.42 (95% CI, 1.35–1.48) for women [5].

#### Etiology

There are several hypotheses that have been proposed to explain the pathogenic steps that are necessary for venous hypertension or venous insufficiency to lead to venous ulceration. In a diseased venous system or failure of the calf muscle pump, venous pressure in the deep system upon ambulation may either fall minimally or not at all [6]. Ultimately, venous hypertension in the deep veins may be transmitted to the superficial system [3,7,8]. Although venous ulcers can occur in patients with only perforator or superficial vein incompetence, they are usually associated with deep venous insufficiency [9,10]. It has been hypothesized that ambulatory venous hypertension leads to ulceration and failure to heal because of senescence of cells in the wound, white blood cell trapping in the microcirculation, fibrin cuffing of the microcirculation, trapping of growth factors and other homeostatic substances in the dermis

disturbing tissue integrity, abnormalities of coagulation cascades, and other mechanisms [1,6,11–15]. Unfortunately, none of these hypotheses has been shown to universally explain why a wound occurs and poorly heals.

#### Risk factors

Most epidemiologic studies on chronic venous insufficiency have recognized several risk factors for venous ulceration including older age, obesity, significant leg trauma, heart disease, congenital absence of valves, previous surgery of varicose veins, primary valve or venous wall degeneration, arteriovenous shunts, and type of employment [16,17]. The degree and pattern of venous insufficiency are also predictive of the development of ulcer formation [18,19]. Insufficiency of the superficial and perforating veins in combination carries a greater risk than insufficiency of the superficial veins alone [4]. There is also a well-recognized association between deep venous thrombosis and venous ulceration [20]. Individuals with venous leg wounds often have varicose veins and other cutaneous findings consistent with venous disease, as well as other medical diseases, such as atherosclerotic vascular disease and diabetes, that can complicate the clinical picture [1,21–23].

#### Prognosis

Venous leg ulcers do not generally lead to the need for amputation, but often result in chronic, malodorous wounds that dramatically impair the quality of life of those afflicted with them. Many venous ulcers heal within 24 weeks of care, but the proportion healed after 24 weeks varies widely in the medical literature. Several studies have shown that the initial healing rate and the percentage change in the venous leg ulcer area in the first 4 weeks of treatment was predictive of complete healing [24–26]. It is important to note that while several studies have shown a peak prevalence between 60 and 80 years of age for venous ulcer disease, 22% of venous ulcer patients will have their first ulcer by age 40 [27–30]. Thus, venous



**Figure 73.1** Venous ulcer of the lower extremity (case scenario 73.1).

ulcers can have a tremendous impact on work productivity and premature disability [30,31]. Some studies have shown that, once diagnosed, the majority of patients will have a recurrence and many will have a long ulcer duration of greater than 1 year [29].

### Aims of treatment

The aims of treatment are to improve the rate of healing and to increase the likelihood that a patient will heal over a given period of time (often 12–24 weeks). Multiple different guidelines have been published by different medical societies for the treatment of venous ulcers [32,33].

### Relevant outcomes

Relevant outcomes include the proportion of wounds healed by the end of the study and the rate of healing.

### Methods of search

Medline, Embase, and the Cochrane Database of Systematic Reviews were searched for the terms “venous ulcer” and “heal” or “treat,” as well as bibliographies of relevant articles and systematic reviews.

## Questions

### What therapies are effective for treating venous leg ulcers?

#### Case scenario 73.1

A 56-year-old woman has an ulcer 25 cm × 6 cm on the medial side of the left ankle (Figure 73.1). The ulcer's red base is covered with yellowish fibrinous debris. On the edges are some signs of reepithelialization. The left lower leg was edematous before use of a limb compression stocking. The limb shows signs of chronic venous

insufficiency: pigmentation, enlargement of the cutaneous veins, and fibrosis. What therapies would be effective treatments?

## Compression

### Benefits

Compression of the lower extremity is one of the oldest and most widely used treatments for venous ulcers. Compression aids venous return, and different methods include stockings, single and multi-layer bandages (both elastic and inelastic), and pumps.

An updated Cochrane collaborative review has evaluated the role of compression in the treatment of venous ulcers [34]. This review included 39 trials using a number of different compression methods. Seven trials compared compression with no compression, and demonstrated that venous ulcers heal more rapidly with compression than without. Of these, two trials evaluated compression using an Unna boot versus no compression. Both studies demonstrated a benefit of compression. Five additional studies compared compression bandages with noncompressive bandages or usual care and demonstrated a benefit. Findings from six trials of single-component compression suggested that this strategy was less effective than multicomponent compression. Seven trials with evidence of using two-component and three-component compression systems showed better outcomes when an elastic component was included. Evidence from three trials with different versions of compression with four-component systems suggested similar effectiveness, but it was difficult to compare the four-layer bandage with the Unna boot because of differences in the paste systems. The four-layer bandage was found to be more clinically effective than multicomponent systems comprising a short-stretch bandage. It is important to point out that in another study not included in the Cochrane review, in a subgroup of the hardest to heal patients, the four-layered bandage was superior [35].

This Cochrane collaborative review did assess cost data that had been included in seven trials and found only one study suggesting that the four-layer bandage was more cost-effective. Several trials assessed health-related quality of life and pain, either as a stand-alone outcome or as part of the assessment of adverse events, and there were no differences found between treatment groups.

### Complications

Complication rates are not usually noted in trial reports, partly because compression therapy is generally benign. Inexpertly applied high compression could lead to soft tissue damage, the development of additional wounds, and potentially amputation, although the chance of this occurring is remote.

### Comment

Compression has been the mainstay of therapy for venous ulcers, and with good reason. It is clear that the overall take away from the medical literature is that compression is superior to no compression in treating venous ulcers. In addition, multicomponent systems are more effective than single-component systems, and multicomponent systems appear to perform better when they are mainly composed of elastic constituents. The method used to apply these bandages is important, and there is some suggestion that the ability to apply compression bandages effectively varies widely. Compression therapy should not be used in patients with an impeded blood supply to the lower extremities. Finally, it is important to note that, in all of these studies of compression, the selection of the bandage directly applied to the wound at a minimum

is to maintain it in a moist state. Very few quality randomized studies exist that compare wound bandages, and this topic is beyond the scope of this chapter. In addition, in practice, health-care providers often change their choice of wound bandage during the course of therapy depending on the properties of the bandage and the wound's status.

### **Implications for clinical practice**

Compression represents the cornerstone of the clinical management of patients with venous ulcers. Most studies evaluating novel therapies for venous ulcers use compression as the standard care regimen (Level I).

## **Pentoxifylline**

### **Benefits**

Pentoxifylline is a trisubstituted xanthine derivative that has been used to treat a variety of systemic disorders, most notably intermittent claudication. Theoretically, its beneficial effects in vaso-occlusive disease could extend to therapy for venous ulcers. A Cochrane collaborative review has addressed the efficacy of pentoxifylline for the treatment of venous ulcers [36]. Twelve trials, including 864 patients, were included in the Cochrane review. Of note, only seven of the trials included compression therapy in both the pentoxifylline and placebo groups. Combining the data from the 11 trials that compared pentoxifylline (in varying doses) with placebo, pentoxifylline demonstrated a beneficial effect. Most of the studies used the probability of healing by 24 weeks as the end point. The relative risk of healing with pentoxifylline versus placebo was 1.70 (95% CI, 1.30–2.24). A separate examination of just the trials that compared pentoxifylline plus compression with placebo plus compression also showed a benefit of pentoxifylline therapy with a relative risk of 1.56 (95% CI, 1.14–2.13). Finally, pentoxifylline in the absence of compression appears to be more effective than placebo or no treatment with a relative risk of 2.25 (95% CI, 1.49–3.39).

### **Complications**

Pentoxifylline therapy is associated with an increased risk of side effects, mostly gastrointestinal in nature. These side effects seemed to be tolerated by participants in the studies.

### **Comment**

The Cochrane review authors conclude that pentoxifylline is beneficial either as an adjuvant treatment for venous ulcers with compression or alone where compression cannot be used. It should be pointed out that all the studies included in the meta-analysis did not individually show statistical significance. The dose of pentoxifylline was 400 mg three times daily in all the studies except for one. Even though a beneficial effect in comparison with placebo was noted when limb compression was not used with pentoxifylline, patients treated with pentoxifylline should be treated with compression therapy as well, because limb compression therapy has been shown to increase the baseline chance of healing.

### **Implications for clinical practice**

Pentoxifylline has been shown to increase the relative risk of healing by 50% over compression therapy alone [36]. Clinicians must ultimately decide whether this potential benefit is worth both the practical and the financial cost of pentoxifylline (Level I).

## **Skin grafting**

### **Benefits**

Most venous ulcers respond well to compression therapy. However, some wounds fail to heal with compression therapy alone. One of the options available to the health-care provider is to treat the wound with a skin graft. Grafts can include full-thickness, partial-thickness, allogeneic (cultured), xenografts, and artificial skin (skin equivalent) grafts.

The use of skin grafts for the treatment of venous ulcers is the subject of a Cochrane collaborative review [37]. Overall, 17 trials were identified. Eleven of these trials compared a graft with standard care in which no graft was used. Two trials evaluated split-thickness autografts, six trials evaluated cultured keratinocyte allografts, two compared artificial skin (bilayered skin equivalent) with a dressing, and two compared a single-layer dermal replacement with standard care. The other six trials compared alternative skin grafting techniques. The authors concluded that bilayer tissue-engineered skin replacement, used with compression, increases the rate of healing of venous leg ulcers compared with simple dressings used with compression. They found insufficient evidence for the effectiveness of any other skin graft material or procedure.

It is important to note that 15 of the 17 trials included in this review were underpowered, so that clinically important differences were unlikely to reach statistical significance and be detected. Overall, there were significant concerns regarding the quality of the trials included and this affected the conclusions that the authors could make. In two more recent studies in which patients had venous ulcers refractory in nature to standard care, a heal rate of at least 50% was achieved after skin grafts [38,39].

Graftskin (Apligraf) is a bilayered skin equivalent that includes both dermal and epidermal components. Some health-care providers also call this “artificial skin.” It is manufactured by harvesting neonatal foreskins and extracting both keratinocytes and fibroblasts, which are then separately cultured to create the epidermal and dermal components, respectively. Graftskin has been studied for the treatment of venous leg ulcers. In a study that enrolled 240 patients, the percentage of ulcers healed after 24 weeks was significantly higher in those treated with Graftskin plus standard care (compression) than in those treated with compression alone (57% vs 40%) [40]. Notably, secondary analyses evaluating the relative efficacy of Graftskin in wounds of more than 1 year's duration demonstrated that the benefit of Graftskin was most significant for patients with older wounds (47% vs 19%) [40,41]. Among patients with wounds of less than 1 year's duration, there was no statistically significant difference in the percentage healed after 24 weeks between those treated with Graftskin and those treated with placebo (66% vs 73%) [40,41]. The Cochrane group analyzed these trial data and concluded that the relative risk of healing with artificial skin versus standard dressings was 1.51 (95% CI, 1.22–1.88) [37].

A single multicenter randomized control study also compared the use of porcine extracellular matrix graft (OASIS Wound Material) and a compression bandage with a compression bandage alone [42]. At 12 weeks, significantly more patients in the extracellular matrix group healed (55% vs. 34%;  $P = 0.02$ ).

In a recent phase 2 double-blind randomized placebo-controlled clinical trial, researchers studied a new cellular therapy (HP802-247) based on human growth-arrested neonatal allogeneic fibroblasts and keratinocytes applied with a modified fibrin spray [43]. The study included 228 adults from 28 centers and found a 16% greater reduction in wound size on average compared with vehicle alone at 12 weeks. It also found that 70% of wounds closed in the



treatment group compared with 46% in the control group. All subjects received four-layer compression bandages.

### Complications

A risk of infection, bleeding, and other tissue damage is inherent in any autologous skin grafting procedure. Moreover, there is always an inherent risk that the donor site will prove difficult to heal as well.

Using cultured autologous keratinocytes is likely to delay treatment, because it takes several weeks for the cells to be cultured. Moreover, patients need to undergo a skin biopsy in order to provide the laboratory with the necessary cells.

Artificial skin theoretically could be cultured from samples that are infected with viruses, including human immunodeficiency virus (HIV). Given the aggressive screening associated with this harvesting, however, the chance of infection is remote, although it does remain a possibility that the allogeneic human cells were taken from an HIV-positive but seronegative donor [40].

### Comment

While autologous skin grafts are occasionally used in some centers to aid the closure of recalcitrant wounds, the difficulties associated with harvesting the donor graft, as well as the complexities associated with inducing closure of the grafted site (in addition to the donor site), mean that this procedure cannot be undertaken lightly. Similarly, use of autologous cultured keratinocytes is a time-consuming, expensive, and complex process that demands multiple patient visits and a laboratory capable of culturing the autologous keratinocytes.

Artificial skin for the treatment of venous ulcers is not in widespread use. This may be because of the substantial cost involved. This concern has been addressed in an economics study [44].

### Implications for clinical practice

Standard treatment with infection control, primary dressings, and the application of high-strength compression heals between 30 and 75% of the venous leg ulcers [34]. While most clinicians would not treat all venous ulcers with skin grafts, patients who have wounds recalcitrant to standard treatment could be considered for skin grafts as an adjunct, to improve their likelihood of healing. Of the available skin grafting methods, the use of artificial skin appears to be the most promising, conferring a 29% increase in the likelihood of healing by 24 weeks and an increased rate of healing. These results are based on a randomized controlled trial in patients with recalcitrant venous ulcers [40,41]. However, the short shelf-life of many of these products, the significant costs associated with the therapies, and the theoretical risk of viral infection mean that clinicians need to think carefully before treating patients with artificial skin (Level I).

## Vitamins and minerals

### Benefits

Few practitioners dispute the importance of adequate nutrition for promoting wound healing. However, despite the assumption that vitamin and mineral supplements may aid in healing these wounds, few studies have addressed the potential benefits of supplementation in a rigorous fashion. For example, vitamin C supplements are often prescribed for patients with chronic wounds. Reports evaluating the use of vitamin C as an adjunctive wound-healing agent have

failed to demonstrate a clear benefit of vitamin C supplements in patients with chronic wounds of all types [45,46].

Zinc has been used for more than a century as a topical adjunct for the care of chronic wounds, and Unna incorrectly believed that it was directly responsible for efficacy of his compression bandage. Oral zinc for the treatment of venous ulcers has been addressed in a Cochrane collaborative review evaluating six trials of oral zinc therapy, most of which failed to show a beneficial effect of therapy [47]. Five of these studies included patients with venous ulcers. The doses of zinc varied across studies. One study failed to demonstrate a significant benefit of oral zinc therapy, with a relative risk of healing of 1.5 (95% CI, 0.28–7.93). The remaining studies also failed to show any benefit of zinc therapy.

Topical zinc was evaluated in one study, suggesting improved healing in both arterial and venous ulcers. However, a study in porcine skin suggested that the only beneficial action of zinc on the wound bed was that it inhibited bacterial growth [48].

Several studies have addressed the efficacy of rutosides in decreasing the edema associated with venous insufficiency [49]. Physiologically, it is believed that these agents protect the microcirculation from the increased pressures of ambulatory venous hypertension, thereby preventing edema. A meta-analysis of four studies was published that evaluated a micronized purified flavonoid fraction (MPFF) of *Rutaceae aurantiae* (Daflon) [49]. Basically, 500 mg of MPFF was administered orally twice daily for 2–6 months, which improved the likelihood of a venous leg ulcer healing by about 32% [49].

One case-control study of 85 patients from Brazil looked at the prevalence of vitamin D deficiency in those with venous leg ulcers compared with a control population. They found a higher prevalence of vitamin D deficiency in patients with chronic venous leg ulcers than in controls. The authors admit that more studies need to be done before drawing conclusions [50].

### Complications

There are few side effects associated with vitamin or mineral therapy for venous ulcers.

### Comment

There is a lack of supporting evidence for the supplementary use of vitamin C, zinc, or vitamin D. No studies have effectively evaluated the role of daily multivitamins in patients with chronic wounds. Rutosides may be helpful in edema reduction.

### Implications for clinical practice

Vitamin supplementation is common and relatively benign. Reasonable evidence exists to support the use of rutosides (Level I).

## Ultrasound, laser, and electromagnetic therapy

### Benefits

Laser therapy using a variety of different lasers, ultrasound, and electromagnetic therapy have been proposed as adjunct treatments for venous leg ulcers. Low-level lasers, ultrasound, and electromagnets have been shown to stimulate cellular function, leading to increased protein synthesis and fibroblast and macrophage proliferation.

Ultrasound, laser therapy, and electromagnetic therapy for venous ulcers are the subject of Cochrane collaborative reviews including eight, four, and three trials, respectively [51–53]. None of

the ultrasound studies found a statistically significant treatment effect [52]. In addition, a more recent randomized controlled trial looking at the use of weekly, low-dose, high-frequency ultrasound during dressing changes for hard-to-heal ulcers in addition to standard care did not increase ulcer healing rates [54]. The results of the laser studies were pooled in the Cochrane review and failed to demonstrate a significant benefit of laser therapy, with a relative risk of 1.21 (95% CI, 0.73–2.03) [53]. The results of the electromagnetic therapy also did not demonstrate a statistically significant benefit [51]. However, these are all active areas of research. This is especially true for electromagnetic therapy, where it is also important to note that not all modalities use the same type, dose, or duration of electromagnetic field.

### **Complications**

Complications occur very rarely with these therapies when therapy is administered by well-trained and experienced staff.

### **Comment**

There is some suggestion that laser therapy and electromagnetic therapy may have an effect on end points other than chance of healing; for example, pain at the wound site and the amount of granulation tissue. The use and meaningfulness of these end points remains an area in need of further investigation.

### **Implications for clinical practice**

There is currently insufficient evidence to support the use of ultrasound, low-level laser, and electromagnetic therapy in treating venous ulcers. Further well-designed trials are needed before these modalities should be widely adopted (Level I).

## **Intermittent pneumatic compression**

### **Benefits**

Intermittent pneumatic compression has been used for a number of indications. Since the underlying cause of venous ulceration is postulated to involve deficient blood return in the calf muscle pump, it has been suggested that intermittent pneumatic compression could improve the healing rates of venous ulcers by improving venous return (i.e., acting as a form of lower limb compression).

Intermittent pneumatic compression for the treatment of venous ulcers has been the subject of a Cochrane collaborative review [55]. This review evaluated seven randomized controlled trials of intermittent pneumatic compression for the treatment of venous ulcers. One trial of 45 patients compared intermittent pneumatic compression plus standard limb compression with standard limb compression alone and found a significant benefit in the intermittent pneumatic compression plus standard compression group, with a relative risk of healing of 11.4 (95% CI, 1.6–82). Three other small trials (122 people altogether) failed to find a significant benefit of intermittent pneumatic compression plus standard compression over standard compression alone. Notably, the duration of therapy with intermittent pneumatic compression in these trials varied considerably. Moreover, the study end points differed substantially. One small study compared intermittent pneumatic compression alone (i.e., without standard compression) with standard compression, and failed to show a significant difference between the groups.

### **Complications**

There are few real complications with intermittent pneumatic compression; as long as the equipment is properly set up, patients would not be expected to suffer any injuries.

### **Comment**

Intermittent pneumatic compression may be beneficial as an adjunct to standard limb compression, but this has yet to be conclusively demonstrated. One of the larger studies noted in the Cochrane review did demonstrate a benefit, but the standard compression used was graduated compression stockings – in contrast to the Unna boot used in another study, which failed to show a significant difference in the proportion of ulcers healed after 6 months. Of note, both studies demonstrated an increase in the actual rate of healing, suggesting that the different study end points (3 vs 6 months) may have played a role in the differing results.

The size and method of use of the equipment requires the patient to remain in a single place for the duration of therapy. The equipment is also costly.

### **Implications for clinical practice**

Intermittent pneumatic compression may increase the rate of wound healing for patients already treated with standard compression. In addition, delivering the intermittent pneumatic compression in a rapid manner by inflating and deflating the device more quickly results in better ulcer healing. However, further study is needed to discover the definitive effects of this device on healing (Level I).

## **What therapies are effective in reducing the risk of recurrence of venous leg ulcers?**

### **Compression**

#### **Benefits**

Compression therapy has been demonstrated to be an effective therapy for increasing the likelihood that a patient with venous ulcers will heal after 12–24 weeks. Since many venous ulcer patients have recurrent ulcers even after they have successfully healed, a pressing question remains as to whether continued compression after wound healing could reduce the likelihood of recurrent venous ulcer formation.

A Cochrane collaborative review has evaluated compression as a treatment for preventing the recurrence of venous ulcers [56]. This systematic review found one study (153 patients) directly comparing the incidence of recurrent ulcers in patients who did and did not use compression. This study found that compression significantly reduced ulcer recurrence at 6 months with a relative risk reduction of 54% (95% CI, 24–72%). Three other studies were included in the systematic review. One study compared medium-compression and high-compression stockings and did not find a significant difference between the recurrence rates in these two groups. Another study assessed ulcer recurrence at 3-year follow-up and found that high-compression hosiery reduced recurrence compared with moderate compression. The final study compared two different types of medium-compression stocking and did not find any significant differences between the two groups. The studies did in fact examine differences in recurrence rates between patients who were and were not compliant with compression stockings, and this demonstrated that patients who were noncompliant with compression were more likely to have recurrent ulcerations [56,57].

#### **Complications**

Complication rates are not usually noted in trials, partly because compression therapy is generally benign. Inexpertly applied high compression could lead to soft-tissue damage, the development of additional wounds, and potentially amputation, although the chance of this occurring is remote.

### Comment

One study has shown that compression reduces the risk of recurrent venous ulceration. Two studies that compared different types of compression found that noncompliant patients had a higher rate of recurrence than those who were compliant with any type of compression regimen [57]. While these data may seem to suggest that ulcers may recur in patients who do not use compression, there are other confounding factors that need to be addressed before this conclusion can be drawn. For example, noncompliant patients may be more or less likely to have serious wounds or to comply with other elements of wound care, including nutrition and avoiding trauma.

The findings of a recent Cochrane review that showed compression significantly reducing ulcer recurrence at 6 months with a relative risk reduction of 54% – coupled with the implications of the noncompliant patients' increased rate of recurrence from earlier trials and the biological plausibility of this therapy – mean that compression is likely to reduce the risk of recurrence of venous leg ulcers. Finally, compression therapy to prevent recurrence is considered by most wound-care experts to be "standard therapy." It might not be ethically justified to conduct a trial comparing limb compression with no limb compression for prevention of recurrent ulceration.

### Implications for clinical practice

Compression appears to reduce the risk of recurrent venous ulceration, and should be recommended for all patients with a history of venous leg ulcers as long as they do not have any other conditions that would make this therapy potentially harmful (e.g., arterial disease) (Level I).

### Surgery

#### Benefits

In the last decade, there have been several randomized controlled trials carried out to assess the efficacies of superficial venous surgery and conservative compression therapy with regard to the healing and recurrence of venous ulcers [58–62]. The Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study and a study by van Gent *et al.* were the largest studies with over a hundred patients or more in each arm [60–62]. The ESCHAR study was a multicenter randomized controlled study that evaluated compression therapy with superficial venous surgery in comparison with compression therapy alone. The long-term data from the ESCHAR study demonstrated after 4 years an improved recurrence rate (31%) after surgery with compression, over compression therapy alone (56%) ( $P < 0.01$ ), but no improvement in healing rate [62]. The van Gent *et al.* study primarily assessed subfascial endoscopic perforator surgery (SEPS) with saphenous surgery as an adjunct and found healing and recurrence rates to be similar, but ulcer-free rates were statistically improved in favor of surgery. In four other studies, SEPS to correct perforator disease was looked at and found to show positive results in ulcer healing and preventing recurrence [63–66]. A recent systematic review found that the role of superficial venous surgery in the management of venous ulcers was associated with similar rates of ulcer healing compared with compression alone, but with less recurrence [67].

Many patients with a venous leg ulcer are elderly and frail and do not want, or are not fit for, venous surgery under general anesthesia. A number of studies have looked at ultrasound-guided foam sclerotherapy as a treatment for venous ulcers [68–73]. This

can be done as an outpatient in the office and works by occluding superficial incompetent veins, thereby removing its contribution to the chronic venous hypertension which is thought to play a role in venous ulceration. It is thought that sclerosing superficial veins may be similar to surgical superficial vein ablation, which when used with an adequate compression system may improve ulcer treatment. The studies at this point are mostly small and observational, so must be interpreted with caution.

### Complications

Almost all venous surgery is performed under general anesthesia, which comes with risks. There is a potential risk of stroke with ultrasound-guided foam sclerotherapy.

### Comment

Current evidence supports the practice of venous surgery to decrease ulcer recurrence. Many patients are not surgical candidates. This makes other options such as ultrasound-guided foam sclerotherapy more attractive, but more studies are needed on this modality.

### Implications for clinical practice

In order to justify venous surgery, it must offer considerable benefits over compression therapy alone in terms of healing rate, recurrence, pain relief, and cost and quality of life to outweigh the potential risks of anesthesia and invasive intervention. The number of potential candidates suitable for venous surgery from the population with venous ulceration is reported to range from less than half to around a third [58,61] (Level I).

### Key points

- Limb compression is the mainstay of therapy for venous leg ulcers, and several studies have shown that compression offers a clear benefit over no compression.
- Pentoxifylline and the flavonoid fraction of *Rutaceae aurantiae* as an adjuvant therapy to limb compression have been shown to increase the likelihood of healing.
- Skin equivalents as an adjuvant therapy to limb compression are associated with an increased likelihood of healing.
- The use of long-term limb compression therapy for those with a healed venous leg ulcer is associated with a decreased rate of recurrence, although poor compliance does compromise the effectiveness of this treatment.

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## Other skin diseases for which trials exist

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### Why a chapter on “everything else”?

Any textbook purporting to guide clinical dermatological practice that fails to cover the majority of skin diseases is open to major criticism. Yet, as Naldi points out in Chapter 1, around 1000–2000 skin conditions have been described to date, and trying to cover them all in just one textbook and in sufficient detail is challenging. In the second edition of this textbook, we aspired to cover as many of the common or important conditions as possible – the words “common” or “important” being defined empirically by the editors on the basis of epidemiological studies and clinical practice around the world. Although we have included more conditions, such as molluscum contagiosum, as discrete chapters in this edition of the textbook, the question remains, what happens to the remaining 1900 or so less common or ignored skin diseases? Many of these other skin conditions may be rare in relative terms, yet collectively they make up a significant component of the dermatologist’s workload, and diagnosing and managing them may take up a disproportionate amount of time relative to the everyday conditions seen in clinical practice. Previous research on the use of Internet resources in dermatology suggests that many hits/requests are concerned with less common skin diseases [1]. From a patient’s perspective, being told that you have a rare skin disease is of little consolation, especially if your doctor knows little about it and you need to find out about effective treatments. So, there is a clear case for including as many less common skin disorders as possible in a book such as this.

In the second edition of this textbook we attempted to “find a home” for all of the randomized controlled trials (RCTs) that we could find on less common skin diseases that were not included in the other disease-based chapters. We included over 70 RCTs on less common conditions, and they are still summarized and available as Web Table 74.1 accompanying this book. One thing we learned from that exercise is that you should never assume that there is no good evidence out there just because a skin disease is rare, as we found informative RCTs on a variety of less common disorders, including perniosis, erythromelalgia, nostalgia parasthetica, and Jessner’s lymphocytic infiltrate. The lesson, therefore, is always to search for high-quality evidence using the methods outlined in Chapter 6.

We have not persisted with the same approach of trying to capture all relevant remaining RCTs for this edition as our initial searches indicated that we would need to include at least another 150 RCTs. The explosion of RCTs over the last 5 years in dermatology is potentially positive, but it has meant that trying to include and summarize them all would take up a book in itself, and its utility to the busy clinician would be limited. Instead, therefore, and true to the spirit of the hierarchy of evidence developed in Chapter 7, we have tried to identify systematic reviews of interventions for those skin diseases not covered in the preceding chapters.

### The importance of mapping all systematic reviews

As well as the requirement to ensure at least some degree of coverage for less common skin diseases in this book, there is a need to point health-care providers and patients to the most reliable sources of evidence; that is, systematic reviews of RCTs. Mapping all of the published systematic reviews for a given disease has been done by our team for atopic eczema and acne, and such maps are available in the public domain from the Centre of Evidence-Based dermatology website <http://www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/resources/index.aspx>. The Cochrane Library is the best source of high-quality systematic reviews in skin diseases [2], although non-Cochrane systematic reviews in dermatology have expanded rapidly [3]. Some of the systematic reviews we have included in this chapter are better than others in terms of quality and scope, but they are nevertheless presented in Web Table 74.1 for users to know (i) that a systematic review has been undertaken on the skin condition in question, (ii) what the review attempted to do, (iii) what the reviewers concluded, and (iv) our own comments on the review.

The search was undertaken in Medline using the skin condition terms listed in Web Table 74.2 and the SIGN filter for systematic review (SR) searching. The search identified keyword searches in the title only, no MeSH terms, no truncation, and no plurals. Of the 92 references identified from the year 2000 to the search date of September 8, 2012, 16 were published in the last 5 years and have been included in this chapter. The data extraction sheet was piloted

by undertaking dual extraction for a small proportion of papers to ensure consistent methodology and completeness of extraction.

## Comment

The quality of the systematic reviews in the table varied from high-quality reviews to reviews with very limited searching, lack of critical appraisal of included studies, and lack of appropriate quantitative data. Nevertheless, the topics of the reviews alone indicate where there is investigator interest in trying to move the field forward, and these include aphthous ulceration (two reviews), chronic foot ulcers (seven), hidradenitis suppurativa (one), and epidermolysis bullosa, lichen sclerosus, morphoea, and pityriasis rosea. None of these topics can be really considered rare skin diseases, and some such as diabetic foot ulcers result in a large amount of population morbidity and health-care costs. Whilst the clinical messages emanating from these systematic reviews (such as erythromycin might be useful for speeding up clearance of pityriasis rosea) are limited and tentative, the main pattern to emerge from the reviews is that studies have been done, but they are too small and poorly reported. They thus provide a strong wake-up call to the dermatology com-

munity to improve the quality of clinical trials, and to always start a trial by seeing what has been done already so that the same old mistakes and designs are not repeated time and time again with increasing confidence.

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### Website tables

Web Table 74.1 Table of systematic reviews included.

Web Table 74.2 Skin conditions included.

<http://www.evidbasedderm.com>





# PART IV

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## The future of evidence-based dermatology

Luigi Naldi, editor



## Where do we go from here?

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### What is the point of discussing evidence-based dermatology?

The idea that doctors should base their treatment decisions on good evidence seems such an obvious notion that it might be taken for granted. Who can really be opposed to the central tenet of evidence-based medicine (EBM) – that of using the best evidence wisely [1]? It is not as if there is one group of dermatologists “over there” practicing evidence-based dermatology (EBD) and another group “over here” who choose not to (Figure 75.1). If the practice of EBD goes without saying, what is point of discussing and promoting EBD?

Medicine is advancing very rapidly, creating major changes in the way dermatologists treat patients. Although there is a clinical need to keep up to date with the exponential growth of such new external evidence, dermatologists frequently fail to keep up if they only rely on an occasional flick through the main dermatology journals or a visit from a pharmaceutical representative. Such a policy leads to a deterioration of knowledge with time. Attempts to

overcome this deficiency by attending clinical education programs have been shown to fail to improve our performance, whereas the practice of EBM has been shown to keep its practitioners up to date [2]. New skills need to be learnt on how to search electronic bibliographic databases efficiently and how to critically appraise the different types of study, as outlined in the “toolbox” section of this book (Part II). Yet time for such activities is very limited in a busy clinical schedule. Dermatologists cannot be expected to read and appraise every new randomized controlled trial published in dermatology, especially as reliance on one early randomized controlled trial can be hazardous, even when published in a prestigious journal [3,4]. Instead, high-quality systematic reviews that have searched for all relevant data are needed to update dermatologists on current best treatments.

It is important to point out that the acquisition of new information technology skills does not mean that they replace the attributes of being a good doctor, such as history-taking and examination skills, often described as the “art” of medicine [5]. As the original definition of EBD developed in Chapter 2 implies, the practice of EBM is an integration of knowledge management skills with clinical skills. The aim is to create an emergent, knowledgeable, up-to-date, skillful, caring, and efficient doctor.



**Figure 75.1** It's not as if there are two distinct groups of dermatologists separated by a brick wall: one evidence based and the other not. All dermatologists practice EBD to some degree. But like learning how to perform skin surgery, learning the basics of formulating questions, searching, critical appraisal, and interpretations are skills that have to be acquired and practiced.

### What exactly are the advantages of evidence-based dermatology?

#### Being systematic, explicit, and up to date

At the top of the evidence hierarchy tree discussed in Chapter 7 stands the systematic review. Systematic reviews of randomized clinical trials (RCTs) developed after it was realized that traditional reviews were done in quite arbitrary ways [6]. Traditional expert reviews are fine for raising issues for discussion and debate, but they are much less suitable for summarizing treatment effects. The unsystematic approach used in such traditional reviews often means that they are more prone to bias and influence from hidden agendas [6]. Many have written “traditional” review articles in the past containing a biased selection of citations to support predetermined views, and the author confesses to having used the “file drawer” method to search for articles in one of his reviews of atopic eczema in 1995 (Figure 75.2) [7].

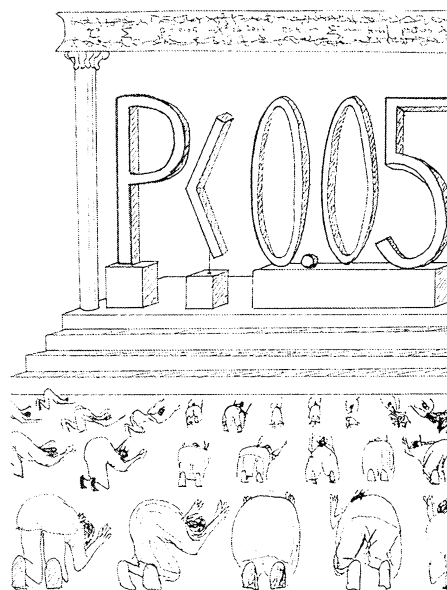


**Figure 75.2** The good old “file drawer” method for locating studies is still the method used and preferred by some authors of traditional “expert” reviews.

Systematic reviews, such as those produced by The Cochrane Collaboration, summarize accurate, up-to-date, high-quality external evidence of the benefits and harms of interventions for treating and preventing human disease [2]. Cochrane reviewers use and refer to a published protocol to describe precisely how they will search, appraise, and synthesize data concerning a specific clinical question, as described in Chapter 8. Such an explicit structure and methodology means that another researcher could replicate the review if necessary, even down to the level of planned subgroup analysis. Like any good randomized controlled trial, the protocol of a good systematic review will be published before the main review is done in order to prevent being driven by data discovered when putting the studies together. For example, it is easy within the context of a systematic review to end up colluding with seven RCTs that have measured a clinically dubious outcome measure by providing a meta-analysis of such data, instead of pointing out that none of the studies had measured what is really important to patients according to a prespecified primary outcome published in a protocol. A recent clinical trial of levamisole measured serum tumor necrosis factor levels as the sole outcome in patients with oral lichen planus rather than symptom control – when did you last see a serum tumor necrosis factor walk into your clinic [8]? An international database of systematic reviews protocols has been set up called PROSPERO with the aim of providing a “one-stop shop” for prospectively registering all systematic reviews in health and social care <http://www.crd.york.ac.uk/Prospéro/>.

### Keeping up to date and increasing precision

Evidence from cardiovascular medicine has shown that doctors have failed to use effective treatments, such as intravenous streptokinase, for acute myocardial infarction even when there was overwhelming evidence for their effectiveness [9]. Conversely, they continued to recommend medicines such as intravenous lidocaine for post-infarction arrhythmias long after the evidence suggested that they were ineffective or even harmful [10]. With over 280 specialist dermatology journals (<http://skin.cochrane.org/>), it has become increasingly difficult for the dermatologist to keep up with the literature [11]. Systematic reviews such as those supported by the Cochrane Skin Group that track down all possible published and unpublished studies are needed to keep dermatologists and other health-care professionals up to date [12]. Cochrane Skin



**Figure 75.3** Research users must overcome the slavish obsession for dividing the results of all clinical trials into those that are statistically significant at the 5% level and those that are not, and instead use confidence intervals to estimate a range of likely effects.

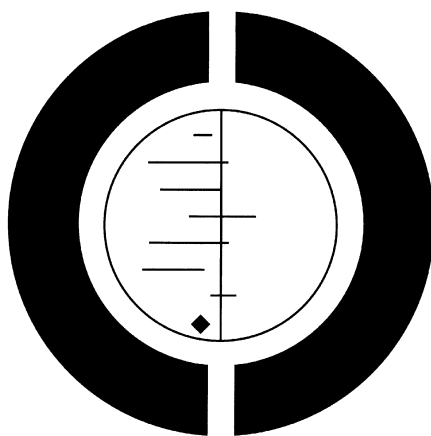
Group reviews have been shown to be of higher quality than non-Cochrane reviews dealing with dermatology [13], and they are also updated as new evidence and criticisms become available. Over 200 systematic reviews now exist on the Cochrane Library that are relevant to skin disease (<http://www.thecochranelibrary.com/view/0/index.html>). Given that systematic reviews have become a rapidly increasing publication type in dermatology [14], some groups have produced maps of systematic reviews (Cochrane and non-Cochrane) relevant to a particular topic such as eczema in the public domain, so that users do not have to waste time searching for such reviews themselves [15].

Systematic reviews can also reduce uncertainty and confusion created by the apparently conflicting results of several small inconclusive studies by combining their results – provided they are sufficiently similar. This may overcome the common tendency to divide all clinical trials into those that are significant at the arbitrary 5% level and those that are not (Figure 75.3), instead of pooling studies that are sufficiently alike in terms of patients, interventions, and outcomes into summary estimates that indicate a range of plausible treatment effects by means of confidence intervals. Studies that reach the “magic”  $P < 0.05$  significance level are commonly claimed as being “positive” and those that fail to reach that level are often considered “negative,” whereas in reality many of the latter trials are far too small to detect even quite large changes [16]. Instead of concluding that such studies are “conflicting,” a meta-analysis performed within the context of a carefully conducted systematic review may show that they are all compatible with a clear overall treatment benefit. The Cochrane Collaboration logo shows a good example of this (Figure 75.4).

### Minimizing bias and identifying research gaps

EBD is very much concerned with reducing bias. Systematic reviews are powerful tools for minimizing bias, because they use explicit methods and because they seek to include all relevant studies rather than studies selected on the basis of their results or how easy they





**Figure 75.4** The Cochrane Collaboration logo depicts a systematic review of seven placebo-controlled trials evaluating the efficacy of a short course of oral corticosteroids for women in premature labor to prevent fetal death. Each horizontal line represents a single RCT; the shorter the line, the more certain are the results. If an RCT touches the vertical line, it means that particular trial found no clear evidence of treatment benefit. The diamond at the bottom represents the combined results, and its position to the left of the vertical line of no treatment difference indicates that the treatment was clearly beneficial in reducing premature infant mortality by 30–50%.

The first of these RCTs was done in 1972. The figure depicts what would have been revealed had a systematic review of the available evidence been done a decade later. By 1991, another seven RCTs had been done. Because no systematic review of these studies had been produced until 1989, most obstetricians had not realized that the treatment was so effective, but instead interpreted each individual study as “conflicting.” As a result, tens of thousands of premature babies around the world have probably died or suffered unnecessarily. This is an example of the human costs of failing to perform an up-to-date systematic review of apparently “conflicting” studies.

(Source: the Cochrane Collaboration.)

are to find. When assessing an intervention for skin disease, the prospective protocol provides an opportunity to state which participants should ideally be studied, which comparators are appropriate, and which outcomes would make a difference clinically and at what time point. Such a “bottom-up” and nonreductionist approach also provides the opportunity of consulting users or consumers (people with a condition, or their carers) to ensure that the perspective of the review and the outcome measures are appropriate. The beneficial role of such service-user involvement is extolled in Chapter 3. Lay summaries are included in Cochrane reviews as the language used by clinicians and researchers is sometimes confusing to consumers (Figure 75.5). Specifying analysis plans in protocols also helps minimize the problem of data-driven reviews that amplify features of studies that may interest the pharmaceutical industry more than patients or health-care professionals. Even for rare skin diseases, producing a systematic review that finds no reliable evidence to inform practice may still be useful, in that it reassures practitioners that they are not missing some important new development [17]. Systematic reviews also have an important role to play in highlighting possible research gaps for future study [18–20], and many funding bodies now will not commit to funding an RCT without a systematic review being done first. It should be noted that, like any other study design, there are good and bad systematic reviews, and even the better ones have room for improvement [21].



**Figure 75.5** Working with patients and carers requires a clear explanation of terms used in studies. For example, the phrase “subjects were broken down by age and sex” is not immediately clear to those working outside of research.

The basic unit of analysis in most systematic reviews is the RCT. As pointed out in Chapter 9, like any study design, RCTs can also be done badly and used in the wrong situations [22,23]. Nevertheless, the RCT remains one of the strongest designs in modern medicine for assessing treatment efficacy, because of its potential to minimize bias [22]. As Bigby points out in his essay on “Snake oil for the 21st century,” studies of inferior design, such as case series, have many times led to overly optimistic claims of treatment efficacy in dermatology that were not borne out by subsequent RCTs [24].

### Influencing the agenda of future dermatology trials

Perhaps the most important and subtle advantage of EBD is its propensity to help change the RCT agenda. It is quite clear from a systematic review of 272 RCTs in atopic eczema that most trials have reflected the agenda of the drug industry in order to license a particular “me-too” product, and that many questions that are important to clinicians and patients remain unanswered [19]. Similar conclusions have been voiced in a review of all RCTs conducted in the field of psoriasis by the European Dermato-Epidemiology Network [25]. Many of the outcome measures used in these trials are clinical scoring systems that may show up minor differences in disease scores in the short term, yet their clinical significance in practice is often obscure, especially in chronic diseases where disease remission and quality of life may be more important. EBD is thus a key instrument in informing the need for comparative effectiveness research using pragmatic clinical trial designs and active comparators when trying to answer questions about which treatment is best [26].

### What are the potential limitations of evidence-based dermatology?

#### The threat of reductionism

Meta-analysis, which refers to the statistical pooling of results drawn from several studies, is prone to dangerous reductionism if used to add studies together which it is not sensible to combine in the first place [27,28]. Thus, before contemplating playing with any statistical techniques, it may be wise to consider not combining

studies of childhood atopic dermatitis with those dealing exclusively with adult atopic dermatitis, as they may differ in terms of etiology, treatment responsiveness, and propensity for adverse effects. It may also be sensible not to combine studies of atopic eczema that evaluate one sort of dietary exclusion with another. It may not make any sense to pool a clinically obscure outcome measure, such as a “doctor-assessed itch,” simply because it was the only outcome that was common to all trials [19]. Meta-analyses are only as good as the data from the individual studies that make up such analyses, and great care needs to be taken to avoid adding together things that should not be combined, especially when the statistical output with lots of numbers and decimal places may give rise to a spurious air of precision to those less experienced in assessing the quality of such analyses. It is for this reason that meta-analyses should always be performed within the context of a systematic review [29].

The involvement of users is another important aspect that may protect against reductionism – for example, in the choice of outcomes. Another criticism of meta-analyses is that, as more and more data are pooled and aggregated, it becomes more difficult to apply such “average” summary measures to individual patients – in other words, EBM applies to populations and not to individuals [30]. This is a somewhat specious argument, given that extrapolation from groups to individuals is a paradox that is fundamental to all scientific studies on groups of people. The paradox of groups and individuals is also applicable to “clinical experience,” which by definition relies on recall of aggregated experiences with groups of patients. It can also be argued that combining several studies containing a broad range of people with different ethnic backgrounds, sex, and co-morbidities actually *increases* external validity to a wider and more typical group of patients, rather than relying on a single trial that describes a narrow range of trial participants.

Reductionism can also occur if EBD practitioners become too preoccupied with the critical appraisal of research without considering the many human factors that are central to the successful practice of EBD as introduced in Chapter 2. Hajjaj *et al.* produce a useful summary of nonclinical influences beyond diagnosis and disease severity that may determine why a gap often exists between practice guidelines and clinical practice [31]. Eaglstein also refers to such a research-practice gap and suggests that a number of physician cognition patterns may be responsible, such as bias against the beneficial, omission bias, multiple alternative bias, and preference for indirect harms [32].

## Cheating

As with any research methodology, it is possible for those with a vested interest to twist the methods and conclusions of a systematic review to their own advantage [33]. Thus, one could conveniently fail to include one crucial study that contradicted the results one wanted to show, or if the study is declared within the review one could find a weak excuse to exclude it post hoc. Because many trials never see the light of day in terms of publication, or are held as “data on file” or just held back by some pharmaceutical companies [34], it is possible for a review to include or exclude such additional unpublished data in a way that favors the product [35]. As with any written document assessing drug treatments, there is plenty of scope for undue emphasis on positive effects and lack of discussion of relevant adverse events. Readers need to develop a “good nose” for what constitutes a good systematic review and clinical trial; some pointers are given in Chapters 8 and 9. This includes starting with a peep at the acknowledgments to see who sponsored the

review or study and assess possible conflicts of interest [36,37] – if, in fact, sponsorship has been declared [38,39].

## Overemphasis on randomized clinical trials

Whilst RCTs may be the most robust study design for minimizing bias in conventional evaluation of the effectiveness of interventions for skin diseases, they have their limitations [40]. In some circumstances, it may be impossible or unethical to perform an RCT. For example, it is unlikely that mothers will agree to be randomized to breastfeeding or bottle-feeding to see whether either prevents atopic eczema. Similarly, it would be impractical to randomize medical students to one form of education and others to another within the same class, because they would not be blinded to the interventions, and there might be considerable “contamination” of the intervention from one group as students talk together. Just because a study is an RCT does not mean that it is a good RCT, and attention to quality and relevance is important, rather than just blindly following the concept of the hierarchy of evidence. Rare but serious events, which are extremely important when evaluating the pros and cons of a new treatment, are not well characterized within RCTs, but instead require other approaches such as case reports, case-control studies, and wide-scale pharmaceutical surveillance methods, as Naldi points out in Chapter 10. Frequently, there is asymmetry in the way that systematic reviews devote a lot of space to treatment efficacy and less or none to issues such as potentially serious side effects [41].

The concept of only using RCTs as the basic building blocks of evidence for systematic reviews has been criticized because it implies that all other evidence that contributes to our understanding of treatment efficacy, such as case series, case reports, and “clinical experience,” are not valid [42]. This is clearly inappropriate. Ideally, the totality of evidence should be considered when conducting a systematic review, so that evidence from observational studies can contribute to the conclusions from RCTs. Approaches such as hierarchical modeling, likelihood estimations, and Bayesian statistics have been used in attempts to address these gaps. It is likely that the concept of a good informative study design is more of a continuum representing the risk of bias, rather than a dichotomy of “good” (i.e., RCTs) and “bad” (e.g., a large case series). This continuum needs to be tempered by the added but crucial dimension of study quality.

Another potential drawback of only incorporating RCTs into systematic reviews is that older traditional therapies, such as curettage and electrocautery for actinic keratosis, which were rarely assessed to the same RCT standards as modern therapies when first introduced but which have stood the test of time, will often lose out to newer industry-funded and more expensive treatment simply because they fail to pass the required level of evidence [43]. Lack of evidence of a well-established treatment does not necessarily imply that such treatments are inferior, although it is always desirable to test such treatments as active comparators when new treatments are introduced, as has recently been done with topical imiquimod cream against standard excisional surgery for low-risk basal cell carcinoma [44].

There are challenges, therefore, for future systematic reviewers to find ways of incorporating informative data from nonrandomized studies, and methodology groups addressing such issues exist within the Cochrane Collaboration. In the meantime, it is best to walk before running, by adhering to the RCT as the basic study design for assessing treatment efficacy in dermatology, at least until better methodological approaches have evolved.

## Reviews always end with the phrase “insufficient evidence”

A common criticism of Cochrane skin reviews by dermatology trainees is that they always end up with the same conclusion: that there is “insufficient evidence” to inform current practice. Whilst this may be true for some reviews, a glance at the reviews in the Cochrane Database of Systematic Reviews shows that at least 40% of those relevant to a practicing dermatologist make specific and clear recommendations for therapy [45]. Even “null reviews” that do not find any good evidence to make specific treatment recommendations have their uses. Thus, a systematic review evaluating the evidence for antistreptococcal treatments for guttate psoriasis found no reliable evidence, despite confident textbook recommendations in favor of such a treatment approach [20]. Not only does such a review identify a major gap needing research, but it also reassures doctors and their patients that they are not missing some important study. It empowers doctors to feel more confident in relying on other levels of evidence, such as case series and empirical reasoning based on mechanism, until better studies are done. It also empowers patients with guttate psoriasis, by allowing them to challenge doctors who insist that they must take prolonged courses of antibiotics or who threaten to take out their tonsils (Figure 75.6).

## Evidence-based paralysis

Absence of RCT evidence does not mean that dermatologists should become paralyzed into doing nothing – so-called therapeutic nihilism [46]. Failure to find any RCTs for the treatment of acne agminata, for instance, does not mean that patients should be told to go away because there is no treatment. It is possible that a well-conducted case series exists, or a convincing case report, or simply the sharing of anecdotal evidence from a senior colleague. All forms of evidence are entirely appropriate to use in the absence of better sources. It is just that, for many years, the evidence hierarchy has been inverted in everyday dermatology practice: starting with muddling along and experimenting on individual patients on empirical grounds, or asking a colleague, or referring to an out-of-date textbook.



**Figure 75.6** One Cochrane systematic review found no good evidence to support the use of antistreptococcal interventions (prolonged antibiotics or tonsillectomy) for treating guttate psoriasis. Sometimes such a “negative” systematic review can be useful, in that it can empower patients to question doctors on the evidential basis for their treatment decisions.

## Evidence not up to date and poor primary data

Whilst it is the aspiration of the Cochrane Collaboration to update all of its systematic reviews periodically as new primary data emerge, the reality is that such updating activity is incomplete, which is not surprising given that it is largely a voluntary activity. Keeping right up to date remains a challenge, and those using systematic reviews often need to undertake additional electronic searches to make sure that no new key studies have emerged since the reviews as a result.

Although the methods of undertaking systematic reviews have become increasingly sophisticated, the raw materials of reliable data are often lacking [47], and it will take some time before the field of dermatology recognizes the importance of good trial design, prospective trial and systematic review registration, and complete reporting. Some promising signs have emerged [48], but it is too little and too late for many research users. Reducing future research wastage by encouraging clinicians and patients to prioritize research questions [49,50], ensuring good study designs that minimize bias, and making sure that all results are published and that they are published fully and honestly and interpreted in the context of other relevant research are all needed urgently if medical and dermatological research is to hold any credibility and trust with the patients who volunteer to participate in such research.

## Progress and future prospects for evidence-based dermatology

The potential limitations of EBD are diverse and only partly justified. Some (such as inadequate coverage) are a function of time, while some (such as reductionism, a refusal to consider non-RCT evidence, and cheating) belong predominantly to those conducting and publishing systematic reviews. Other aspects, such as evidence-based paralysis or failure to use available evidence, are a misunderstanding or form of neglect that belongs to those using the evidence. Many of the commonly cited criticisms, such as “all skin reviews are negative” or “EBD ignores patient values,” fall down when challenged by objective data and when the original tenets of evidence-based practice are revisited.

## Mapping priorities, collaborating and thinking globally

Too much research has been conducted in isolation at the whim of academics and industry leaders without any form of joined-up thinking. Liberati, founder of the Italian Cochrane Centre, who eventually succumbed to myeloma, found it so frustrating to witness the “the butterfly behaviour of researchers, moving onto the next flower well before the previous one has been fully exploited” [51]. More emphasis should be placed on mapping the entire evidence base of ongoing reviews and clinical trials in each major dermatological disease, as is being done for atopic eczema with maps of systematic reviews [15] and the GREAT database (Global Resource of Eczema Trials) [52]. Undertaking network meta-analyses of all available studies permits key comparisons of interventions that might have been deliberately avoided in primary research, as well as allowing a glimpse of what has been done and where more research needs to be done [53]. Working with patient groups in priority-setting exercises is also a good place to start before rushing off to do more research that may turn out to be of little clinical value or, worse still, duplicates existing or ongoing research [50]. Collaboration outside of traditional institutional



territories is essential to answer the big clinical trial questions in dermatology research, especially for less common skin disorders. Thus, the UK Dermatology Clinical Trials Network has gathered the help of 50 recruiting centers in order to determine whether oral tetracyclines have a useful role in the treatment of bullous pemphigoid [54] or which is the most effective treatment of pyoderma gangrenosum [55]. Other countries have shown interest in developing similar country-specific or disease-specific networks, and a website has been created to provide a focus for such international efforts: <http://www.ifdctn.org/ifdctn/index.aspx>. Such networks are also important vehicles in the “democratization of research” into the coal face of the clinical community who are well placed to take more ownership in choosing the right questions, delivering the research and changing their practice on the basis of the study results [56].

### So, is it all just another fashion that will come and go?

For some, the whole concept of EBD might seem like just another new management-driven fad that will come and go like others [24]. Perhaps it is the human factor of shame in admitting that some of our previous treatment beliefs might be wrong that prevents progress – the “elephant in the front room” that doctors keep bumping into without seeing [57]. Yet what is the alternative to EBD? Is it anecdote-based medicine (“I once treated a patient with such and such with remarkable effect . . .”), entropy-based medicine (“let’s try this cream today. . .”), arrogance-based medicine (“I know best”), or propaganda-based dermatology driven by powerful cartels with vested interests? It is hard to believe that any caring dermatologist would not wish to base their treatments on the best external evidence. Two studies have already shown that dermatologists use as much high-quality external evidence to inform their treatment decisions as other specialists do [58,59]. Since the last edition of this book, considerable progress has been made to incorporate EBM into continual professional development and clinical practice. Major dermatology journals, including the *Journal of Investigative Dermatology*, *Archives of Dermatology* (now *JAMA Dermatology*), the *British Journal of Dermatology*, the *Journal of the American Academy of Dermatology*, and the *Indian Journal of Dermatology*, have been forthright in their insistence on prospective trial registration and adoption of good trial reporting guidance from the Consolidated Standards of Reporting Trials (CONSORT) statement for improving the reporting of trials. The *Journal of the American Academy of Dermatology* now runs a section on summaries of Cochrane reviews [60], and the *British Journal of Dermatology* now promotes submissions of critically appraised topics rather than a sea of case reports [61]. Taboo issues, such as conflict of interest, are now being openly discussed at dermatology journals and meetings, with appropriate declarations during presentations [36]. EBM principles form part of many teaching curricula in dermatology, and specific courses that use dermatological examples are appearing at major dermatology meetings and centers (<http://www.bees.org.uk/courses/about/>). Dermatology is no longer a backwater for EBM, although it still has a long way to go. One of the most difficult challenges common to all EBM is how to ensure that the findings of well-conducted studies are incorporated into practice [62].

It is reasonable at this point to ask, “What is the evidence for EBD?” An entire theme issue of the *British Medical Journal* was dedicated to this topic in 2004, although it came up with more questions than answers, mainly due to the methodological difficul-

ties in linking EBM teaching to clinical outcomes [63]. In some senses, it is a tautological question, as it implies that there is a group of doctors who are evidence based and another group who are not, as pointed out at the start of this chapter (Figure 75.1) – whereas the reality is that all belong to a dynamic and complex continuum. Such a continuum makes the evaluation of “EBM” as an intervention in its own right almost impossible to assess by means of an RCT. In-depth discussions on the epistemology and ethical issues posed by the name and concept of EBM can be found elsewhere [27,46,47,64,65].

Trying to divide physicians into those who are evidence based and those who are not is a form of binary thought disorder and not an accurate reflection of real life. Like Molière’s bourgeois gentilhomme, who, after 40 years, discovered that he had been speaking prose without realizing it, many dermatologists have been practicing, and will continue to practice, high-quality EBD. Yet all health-care professionals need to learn new skills in searching, appraising, and translating the evidence. That part is now up to you.

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## Note:

Cross-references are implied between the individual drugs and the drug groups.

*vs* denotes differential diagnosis or comparisons.

Page numbers in *italics* represent figures, those in **bold** represent tables, or boxes.

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